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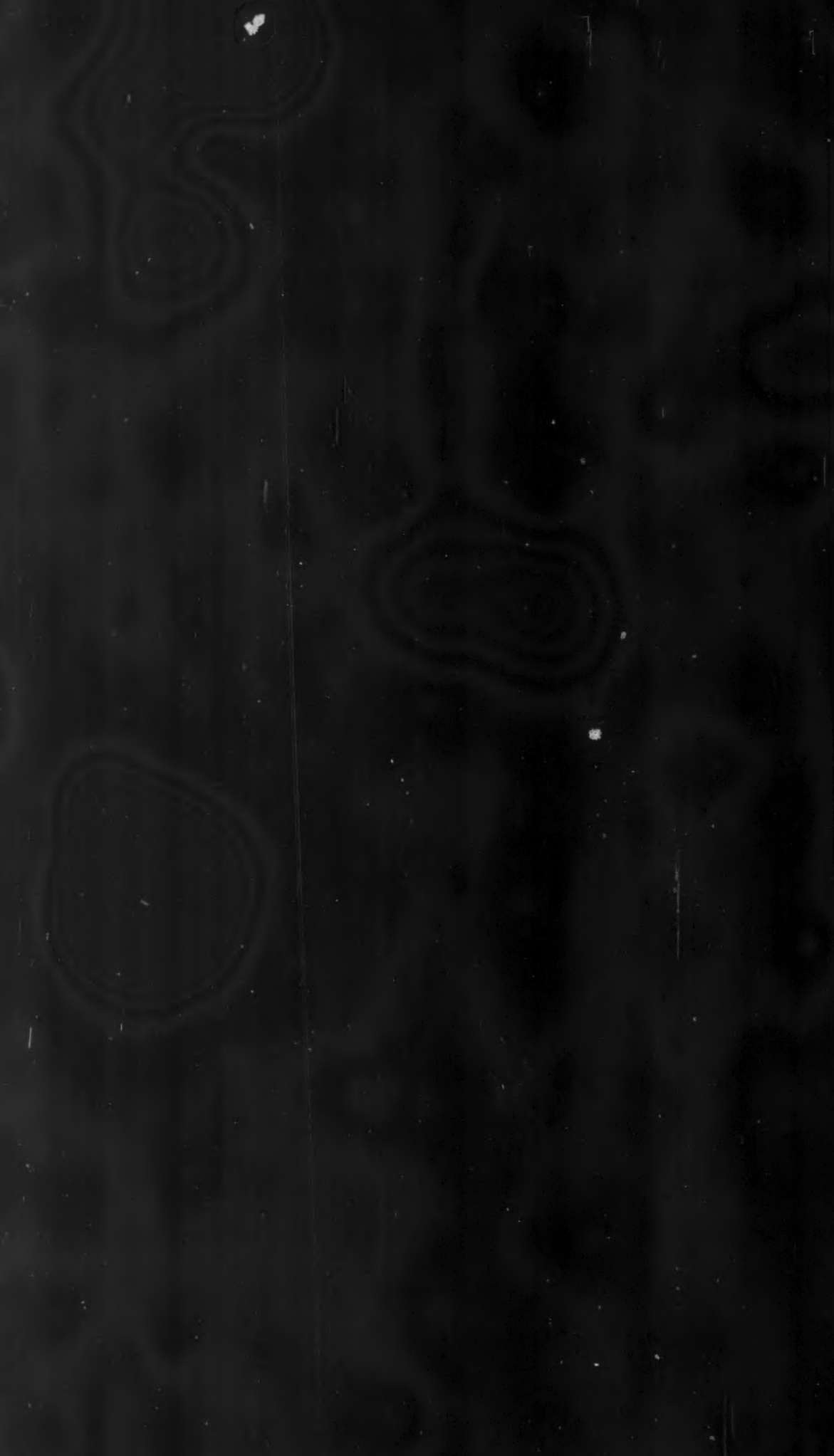

STEPHEN WALTER RANSON, 1880–1942

An Appreciation

Stephen Walter Ranson, Professor of Neurology and Director of the Institute of Neurology of the Northwestern University Medical School, was a distinguished contributor to anatomical and physiological science during the past four decades. After receiving his baccalaureate at the University of Minnesota at the age of 22, he, in the next five years received successively the M.S., Ph.D. and the M.D. After two further years of academic and medical apprenticeship he commenced his academic career at Northwestern Medical School in 1909 and three years later was appointed to the chair of anatomy. In 1928 he was selected to direct the newly founded Institute of Neurology.

His life was devoted to the study of the minute and barely attainable, and he discovered where others have looked and not beheld. Like the astronomer who knows the existence of a star before it is seen, he early deduced the existence of a system of nerve fibers which had escaped the microscope, and by the development of special stains brought them into view. To the study of these fine nerve fibers he, and others returned again and again, until their connection with pains that have baffled the physician and surgeon is finally becoming clear.

In his recent years he addressed himself to the part of the nervous system, minute and deeply concealed in the brain, which controls the functions of the human body on which life depends. To this he brought a device which enabled him to penetrate deeply into the substance of the brain, to stimulate or to destroy, and to chart with the accuracy of the surveyor the functional topography of the brain. The closeness of his search and the exactness of technique was again rewarded by disclosing the function of another system of nerve fibers—fibers which pass directly from the brain to the pituitary gland and control its secretion.

T.C.R.

TEMPERATURE EFFECTS ON REFLEXES OF ISOLATED SPINAL CORD

HEAT PARALYSIS AND COLD PARALYSIS

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(Received for publication May 12, 1942)

EFFECTS of temperature on reflexes of frogs have been studied in experiments in which temperature changes affected the entire body. No experiments are recorded in which the influence of temperature has been confined to the nervous system without affecting muscles and receptors. Employing a preparation of the vertebral column containing the spinal cord isolated from the body, except by the iliac nerves which maintain nervous communication with the legs, and by putting the vertebral column in baths of Ringer's solution at different temperatures, it has been shown in Brazilian frogs (*Leptodactylus ocellatus*), that the form and also resistance of the reflexes present constant alterations at temperatures above and below an average temperature of about 18°C. It was also found that the curves of resistance at different temperatures show quantitative variations when obtained in different seasons of the year (1).

In this paper are related the results of similar experiments in American frogs (*Rana pipiens*) conducted a year ago at Yale University. Brazilian frogs develop convulsive attacks if the spinal cord is cooled below 8.5°C. This fact does not permit experiments on the reflexes at these low temperatures. However, in American as in European frogs, this attack is normally produced only at temperatures below 0°C. Using *Rana pipiens* it has now been possible to enlarge the limits of temperatures employed as it happened before in the experiments conducted at Paris.

APPARATUS AND METHODS

The preparation is made just before each experiment. After separation of the spinal cord from the superior centres, the animal is pinned as usual on a cork plate. The skin is cut along the dorsal median line. After cutting the aponeuroses, the urostyle is picked up with the forceps and the sacro-coccygeal and ilio-coccygeal muscles severed. The lumbar nerves are dissected and isolated. It is then possible to separate the vertebral column from the body. The legs with the isolated iliac bones are attached by threads to a horizontal support if the experiment is intended to be a simple observation, or on the plate of a myograph if records are wanted. Figure 1 shows schematically the experimental procedure to obtain Ringer's baths at different temperatures. The essential part is the small apparatus A. The Ringer's solution in the upper part is isolated from the circulating liquid (water; or water, ice and salt for low temperatures) coming from flask F. Careful regulation of the output and of the temperature of the water permits having the Ringer's baths at the desired temperature.

In experiments conducted during the winter in New Haven, the laboratory's atmosphere was too dry. Nerves in contact with the rim of the bowl containing the Ringer's bath were soon excited by Ringer's solution which had previously overflowed and by losing water, had become a hypertonic solution. This happens particularly in experiments at high temperatures. The nerve's excitation is shown by spontaneous contractions of the leg

muscles. To avoid these contractions it is sufficient to wash the nerves frequently with Ringer's solution, and the skin of the legs with fresh water. In these experiments mechanical excitations of feet and legs were employed. After a certain time, when the reflexes are weakening, the excitations must be repeated and summated. In this period, one single excitation can be inefficient, while repeated excitations still produce strong reflexes. Disappearance of reflexes is established when the strongest repeated excitations do not provoke any reaction.

Results

Spontaneous movements. In experiments with American frogs, preparations of isolated spinal cord and legs frequently show spontaneous move-

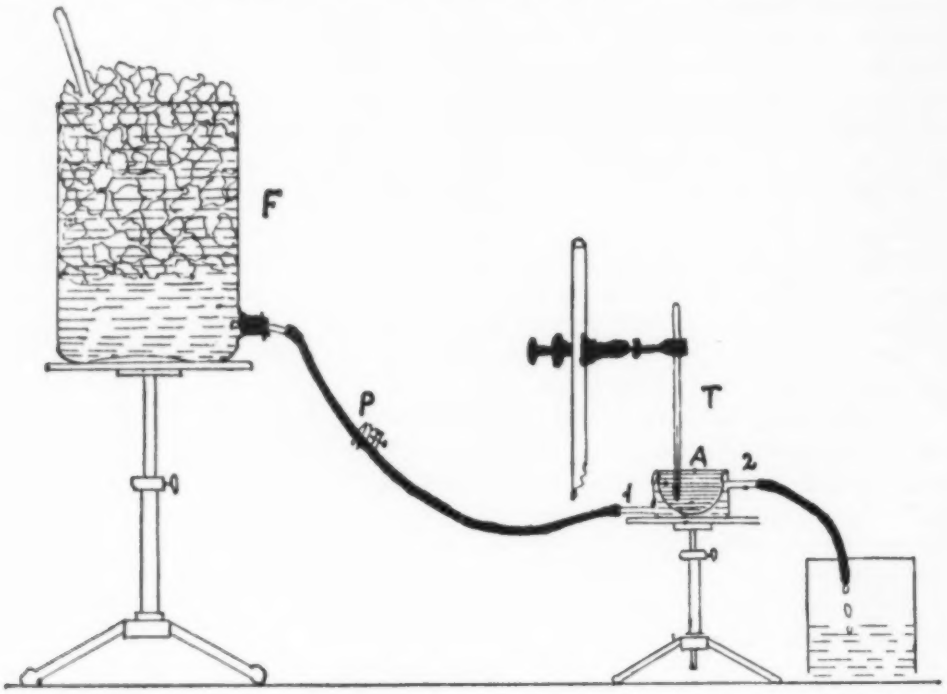

Fig. 1

ments. These movements are well coordinated, and the legs flex and extend alternately. Such reactions can be observed for a few minutes. In some cases, just one leg presents this form of activity while the other one is at rest. Spontaneous coordinated movements are not to be seen when the spinal medulla is in a Ringer's bath at low or high temperatures, below 3.5° or above 21°C. In many cases high temperatures produce strong excitations: the legs react in discoordinated movements that soon disappear. Between 8° and 18°C. spontaneous movements are produced in almost all cases. Perhaps, the spinal cord at these temperatures finds itself in a state of increased excitability and is able to answer to excitations not directly made, but that are due to exposure of the tissues to air.

Alterations of reflexes. In American frogs the reflexes do not show all the

alterations previously observed in Brazilian frogs. However, at low temperatures the same type of alterations are to be observed: flexion is prolonged and the flexed legs shows rapid alternate movements in the different segments; it is a type of clonus produced by cold. However, on the other hand, at high temperature the reversal of reflexes observed in Brazilian frogs, consisting of a change of flexion into active extension, is not seen in American frogs. The reflexes maintain the flexion type until they disappear. In some cases, after flexion, the return of the legs to a normal position is not simply due to relaxation of flexor muscles but to a slight contraction of the extensors.

Exhaustion of reflexes—Heat paralysis and cold paralysis. If the spinal cord is subjected to different temperatures, the reflexes disappear after different time intervals, in direct correlation with the temperature. If the spinal medulla is again put in a Ringer's bath at room temperature immediately after cessation of the activity of the spinal centres under direct action of cold or heat, two different results can be obtained. When in the first part of the experiment, the temperature of the bath is between 14° and 29°C., the reflexes do not return: the spinal centres are exhausted. When the previous temperature is below 14° or above 29°C., the reflexes return normally. Under the action of cold or heat, the lack of action of the medullary centres is not due to exhaustion. The nervous centres are paralysed, and they can present a *heat paralysis* or a *cold paralysis*. Alternate periods of paralysis and activity can be obtained many times in the same preparation. The bath's temperature where paralysis is produced must be sufficiently low or sufficiently high so that the state of paralysis is attained in a short time. After some repetitions of the state of paralysis and recovery, the reflexes are definitively exhausted. For example, in one experiment (Feb. 6), in the Ringer's bath at 35°, the medulla lost all reactions after 3 min.; when removed to another bath at 20°, the reflexes were present again 30 sec. afterwards; a second period of temperature at 35° produced the disappearance of reflexes after 1 min. These reflexes reappeared after the preparation was replaced in the bath at 20°. Finally, the third time that the medulla was subjected to 35°, the reflexes disappeared permanently.

Heat paralysis of the nervous centres has been studied by different methods by other physiologists, Working with the whole frog, Winterstein (2) explained this phenomenon as the result of an asphyxiation of the centres. The results obtained in experiments with the isolated spinal cord do not support this explanation. Control experiments demonstrate that the restoration of reflexes, after the return of the paralysed medulla to normal temperature, is obtained without the contact of the nervous centres with the outside air.

Instead of Ringer's solution, the apparatus for cooling the medulla contained paraffin oil, which is heated to a temperature of 35°C. by the circulation of hot water in the external part of the bowl. Then the communication of the bowl with the flask F is closed and the hot water is replaced by cold water. The oil's temperature is maintained for the necessary time. Putting the medulla of a preparation in the hot oil, after the reflexes have disappeared

the communication with the flask F is opened and the circulation of cold water produces a fall of temperature so that the oil attains 20° in 4 or 5 minutes. The reflexes return with their normal characteristics. Therefore, the spinal cord, which has remained in the oil without contact with the air, is paralysed by heat and recovers from this paralysis only by cooling.

Resistance of reflexes. The time needed for the disappearance of the reflexes is variable with the temperature, and the curves obtained are of similar shape as those previously obtained in Rio de Janeiro and Paris. However, the curves are themselves not superimposable; and in this case, it seems that the action of climate and general conditions of the life of the frogs must be taken into consideration. In the experiments at New Haven, two different curves were obtained (Fig. 2), the first in January at the beginning of the cold weather, and another between February 10 and March 5. The experimental results are reproduced in Table 1 for the first period and Table 2 for the second.

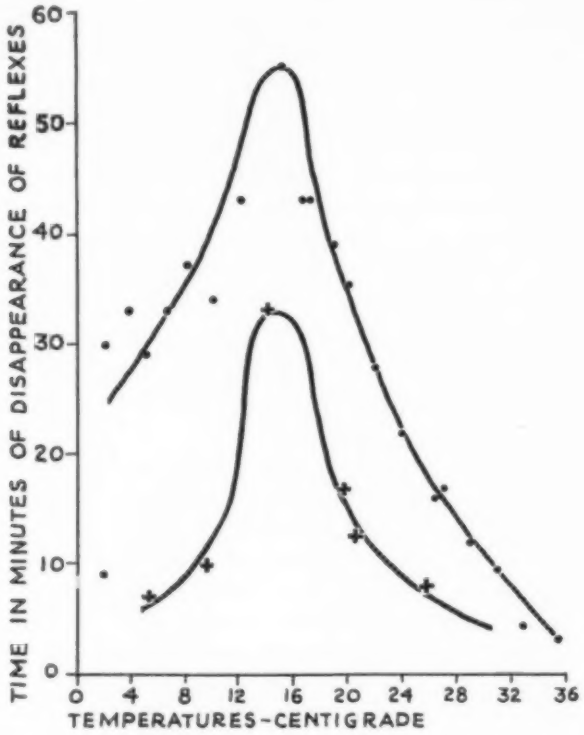

FIG. 2. Curves of the time of disappearance of the reflexes when the isolated medulla is submitted to different temperatures. Plus signs, experiments made in January; black dots, experiments made in February and March.

The time before the disappearance of the reflexes increases with increasing temperatures attaining a maximum at 15°C. on the average, and

Table 1. Time of disappearance of the reflexes in different temperatures, January 13.

Temperatures of the Ringer's baths. (θ) Centigrade	5.5	9.5	14.0	20.5	19.7	25.8
Time of disappearance of the reflexes (t_1) in minutes	7	10	33	12,5	17	8

Table 2. Time of disappearance (t_1) of the reflexes in different temperatures of Ringer's baths (θ), and recovery time (t_2) in baths at room temperature (θ'). The time of exhaustion at room temperature when the medulla is put from the beginning at the Ringer's bath (θ') is t'.

1	2	3	4	5	6
θ	θ'	t'	t_1	t_2	$1-\frac{t_2}{t'}$
2,1	17,0	43	9	28	0,35
2,1	16,5	43	30	36	0,16
3,8	16,5	43	33	30	0,30
5,1	17,0	43	29	26	0,39
6,6	16,8	43	33	26	0,39
8,1	17,0	43	37	23	0,47
10,0	14,7	55	34	12	0,79
12,0	15,0	55	43	5	0,91
14,9	14,9	55	55	0	1,00
16,7	16,7	43	43	0	1,00
17,0	17,0	43	43	0	1,00
19,0	19,0	39	39	0	1,00
20,1	20,1	35	35	0	1,00
22,1	13,8	55	28	0	1,00
24,0	14,8	55	22	0	1,00
26,3	14,9	55	16	0	1,00
27,1	19,0	39	17	0	1,00
29,0	18,0	40	12	5	0,87
31,0	18,9	39	9,5	8,5	0,78
33,1	19,0	39	4,5	20,5	0,48
35,0	17,9	40	3,5	23	0,42

decreasing afterwards with higher temperatures. In these experiments results at high temperatures were more regular than at low. The results were not obtained the same day, but this does not explain the irregularities.

In the middle temperatures the time of resistance is considerable and the question arises whether, in the end, the exhaustion of the reflexes is truly due to an exhaustion of the nerves or nervous centres; or if the muscles deprived of circulation at room temperature are no longer able to react. New experiments demonstrate that this is not the case. Sometimes the total time of resistance of the reflexes is greater than the maximum observed in the curve, if the spinal cord is subjected to a low temperature before and to the middle temperature afterwards. In control experiments all circulation in the posterior half of the body was tied, while the anterior half was in a nearly normal condition. Reflexes were present more than an hour. Finally, Baglioni (3) in experiments with his preparation of spinal medulla isolated and exposed to air, and communicating by the sciatic nerve with the leg cut at level of the knee, has seen that at room temperature the reflexes resist more than two hours.

Localisation of action of heat. Heat paralysis, observed in other ways, has raised the question: Does paralysis result from the action of temperature on the nervous centres, or on the peripheral organs? Experiments of Archangelsky and of Becht (4) have shown that it is the central nervous system that loses its functions under action of high temperatures. In the experiments here reported, the question is more limited. The muscles and skin receptors are not subjected to heating, and the results can be due only to the alteration of the temperature of the nervous centres or the peripheral nerves.

The analysis of this point has been made in several different experiments. The nerve trunks of the preparation were enveloped with cotton, while the vertebral column and the legs were at room temperature. Between the two nerve bundles, and also contained in the cotton envelope was placed one thermometer. The cotton was then soaked with a hot Ringer's solution which was frequently renewed, and in this manner, the temperature was maintained between 32° and 34°C. The reflexes disappeared after 16 min. At this temperature the whole spinal medulla does not react after 4 to 6 min. Disappearance of the reflexes, due to nerve paralysis, takes then three times longer to be produced than central nervous paralysis. In other experiments the two legs of the preparation were separated by a section along the median line. While one leg was in hot Ringer's bath, the other and the medulla were outside the apparatus at room temperature. For example, in one experiment, in the leg heated at 34.5°C. in the bath, the reflexes disappeared after 17 min., while in the other leg they were perfectly normal and strong. At 34.5°C., the spinal cord loses its functions after 2.5 or 3.5 min. In this experiment, the time necessary for paralysis due to the action of the temperature on the peripheral organs, including the nerves, was 5 to 6 times greater than in the case of central paralysis.

Recovery time after heat or cold paralysis. After cold or heat paralysis, the spinal cord being again replaced in baths at room temperature the time intervals during which the reflexes reappear are not constant. In the case of cold paralysis, the recovery time decreases when previous temperature producing paralysis increases; in the case of heat paralysis, the recovery time increases with increasing temperatures. Figures of values obtained are found in column 5 of Table 2.

Discussion

In the conditions of the experiments reported, the spinal cord is contained in the vertebral canal without blood circulation and covered by a thick envelope of tissue. Respiratory exchanges between the nervous centres and the outside air may be completely suppressed. The medullary centres can maintain their functions during the time they dispose of a certain amount of oxygen previously existent, or during the time that carbon dioxide or other substances produced by metabolism do not attain a level where paralysant action manifests itself.

Between 14° and 29°C. the nervous centres' function disappears when

complete exhaustion is attained. Below 15° and above 29°C., nervous centres are paralysed at a moment when they dispose of the reserves, that are able to permit restoration of functions in a normal manner if they are placed again in room temperature. The length of this second period, during which the reflexes recover after a previous paralysis, varies directly with the deviation of the temperature of the paralysing bath from the average. This suggests that the action of this lack of oxygen or of the products of metabolism is not exerted at the same level when the temperatures are different, in the cases of temperatures that produce cold or heat paralysis. These levels decrease with decreasing temperature in the case of cold paralysis, and increase with increasing temperature in the case of heat paralysis.

Taking the metabolism's level attained at average temperatures, when reflexes disappear by exhaustion, as unity, immediately after cold or heat paralysis, the nervous centres have a reserve that is given by the relation t_2/t' (t_2 recovery time; t' time of exhaustion of the reflexes at room temperature θ'). At this moment the level attained by the products of metabolism is $1-t_2/t'$. In column 6 of Table 2 are reported the values of this difference. Plotted on rectangular coördinates, these values form nearly an ascendent straight line for low temperatures, and a descendent straight line for high temperatures.

On the ground that intensity of the tissue metabolism increases when temperature increases, it could be expected that the period of the resistance of the reflexes is greater the lower the temperature. As a matter of fact, experimental curves have not confirmed this assumption; they present one maximum, and below a given temperature the curve descends. This fall can be well explained otherwise than by an alteration of the law of the variation of metabolism in function of the temperature. Paralysis by cold intervenes at a moment when the concentration of the metabolic products is lower than the level for exhaustion of the centres when these are under action of mean temperatures, and this paralysing concentration is decreasing when temperatures decrease.

Conclusions

1. In preparations of isolated spinal cord and legs from American frogs, spontaneous coördinated movements are observed if the temperature is between 3.5° and 21°C.

2. Differences are noted between American and Brazilian frogs in the form of reflexes, when the spinal medulla is subjected to different temperatures.

3. The time of resistance of spinal reflexes at different temperatures, in American frogs, as in frogs previously studied (Brazilian and European frogs), form curves with a maximum for a mean temperature. Below and above this temperature the time of resistance decreases.

4. Position and value of this maximum are dependent on habitual temperatures and conditions in which the frogs are living.

5. Reflex exhaustion is permanent when the spinal cord is subjected to temperatures between 14° and 29°C.

6. Above 29°C., before exhaustion, the spinal centres are paralysed after intervals of time decreasing with increasing temperatures. Recovery is obtained if the spinal medulla is put again in the mean temperature. Heat paralysis is not due to asphyxia, and recovery does not depend of any exchange between nervous centres and the outside atmosphere.

7. Below 14°C., cold paralysis is observed and the time for it to be produced is shorter the lower is the acting temperature. Recovery also is obtained, after paralysis, when the medulla is placed again in the mean temperature. Cold paralysis, as heat paralysis, intervenes before the exhaustion of the centres.

8. Heat and cold paralysis are not due to an interruption of conduction in the nerve or to any action on peripheral organs. Under the action of low or high temperatures the nervous centres cease their functions long before peripheral nerves and organs.

9. The time of disappearance and the time of resistance of the reflexes after recovery from paralysis when the spinal cord is again at room temperatures may give available indications upon conditions of nervous centres at the moment when cold and heat paralysis are produced. At high and low temperatures, nervous centres are paralysed by concentrations of metabolic products, which are ineffective in mean temperatures. The intensity of action of these products is dependent on the temperature.

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ELECTROENCEPHALOGRAM OF DECORTICATE MONKEYS*

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(Received for publication March 15, 1943)

SINCE electrical potentials can be recorded from all active living cells, the pattern of rhythmic potential differences known as the electroencephalogram (EEG) obtained from the complex surface of the brain is probably an algebraical summation of activity within the underlying cells. To understand the nature and composition of this pattern it is therefore of interest to attempt analysis of various anatomical components of the brain which might contribute to its structure.

Recent studies have already given evidence that the subcortical nuclei directly affect the EEG, since, in the monkey, destruction of portions of the basal ganglia causes prompt and permanent changes in the character of the EEG (7, 8), although lesions confined to cortical tissue do not alter it even if an entire hemisphere is removed.

Furthermore, previous investigators had already established the fact that independent rhythms may be obtained from thalamus (11, 1), cerebellum (11), and from the "basal regions" (3, 4, 6). In the present paper are reported the results of further investigation of the interrelationship of cortical and subcortical structures as indicated by their spontaneous electrical activity.

METHOD

Five monkeys (*Macaca mulatta*) were used. In four of these, records were taken first in the normal and finally in the completely decorticate state. Two were chronic preparations and two acute, as it was thought that perhaps the immediate effects of ablation might affect the EEG. However, the results in all four instances were alike. The fifth animal was hemidecorticate throughout the experiment.

A Grass, three-channel ink-writing oscillograph was used. Bipolar silver wire electrodes were placed directly on the tissue in most instances. At other times records were taken from the intact skull. Occasionally monopolar leads were used, the indifferent electrodes being then attached to both ears. All animals were lightly anesthetized with Dial throughout the procedure (0.6 mg. per kg. body weight, given one-half intraperitoneally and one-half intramuscularly). They remained in an even state of anesthesia until the end of each experiment. The decortications, both acute and chronic, were carried out by the same method and surgical technique.

EXPERIMENTAL DATA

In the first three experiments the electrical activity of totally decorticate preparations was investigated.

Expt. 1 (EEG 5) Dec. 4, 1942: A large, nearly mature, male monkey weighing 5.0 kg. had had the left cerebral hemisphere removed one year previously on Nov. 11, 1941, for another purpose. EEG records from the skull over the remaining hemisphere had been normal in the interval. Four days before the present experiment the right cerebral hemisphere was also removed. The animal was then kept in an incubator and tube-fed. Its condition was excellent at the time of the experiment.

* Aided by a grant from the Josiah Macy, Jr. Foundation.

Records made through the skull of the anesthetized animal showed characteristic rhythmic potential differences of rather low amplitude but with a rate of 8–10 per sec. oscillations such as are normal in these animals (Fig. 1).

Next, the bone flap made 4 days previously on the right side was turned back and the electrodes placed on the tissue from which cortex had been previously separated. At this time, before the left basal ganglia were exposed, because this was the first experiment of its kind, various experimental procedures were tried which were subsequently proven

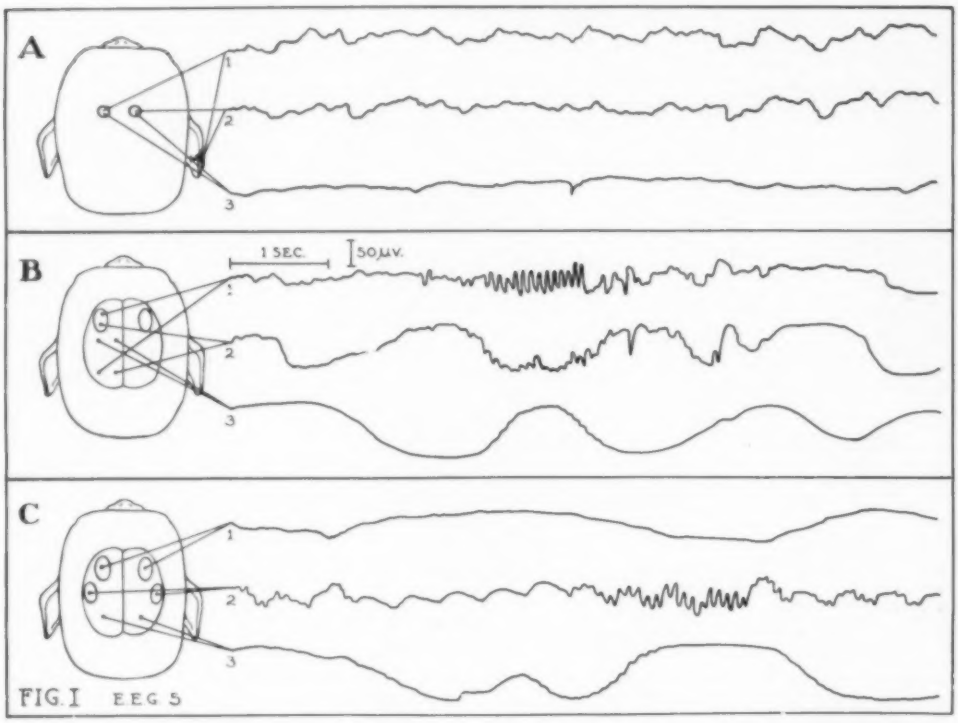

FIG. I EEG 5

irrelevant. The left skull and dura were then removed and leads placed on the right basal ganglia and right side of thalamus. Later they were replaced so as to record simultaneously from the basal ganglia of both sides (Fig. 1). The records thus obtained were unlike those recorded from any other areas and proved later to be characteristic for the caudate and putamen.

From these nuclei the EEGs were of low voltage and displayed a background activity which varied in amplitude but showed a more or less regular rate of oscillation at about 6–8 per second. These resembled in rate the medium frequency waves obtained from cortex but never were complicated by the rapid components found in cortical records.

Superimposed upon the more regular low voltage background activity appeared bursts of much higher amplitude (Fig. 1B). These occurred spontaneously and at irregular intervals varying from every two or three seconds to several minutes. Their character was always the same. Regular rapid spikes suddenly appeared from a record showing little activity. The bursts lasted two to five seconds and increased in both amplitude and rate during the middle of the burst, while beginning and end were both lower and slower. Such bursts were suppressed by any manipulation of the surrounding tissues and, apparently, by loud sound or repetitive light flashes.

In Fig. 1B one such burst is shown. It is recorded strongly from caudate leads (1), less strongly from the putamen (2). In Fig. 1C only the putamen of one side is active.

Records from the 3 animals from which these bursts were obtained all showed that

they might appear only in one portion (caudate or putamen) of one basal ganglion but that, when marked, the entire complex fired synchronously. The basal ganglia of the two sides did not necessarily fire synchronously however. There was never any evidence of bursts of spontaneous activity in thalamus alone, although characteristic potentials appeared from this area also. Leads placed on internal capsule or corpus callosum near the basal ganglia did not record such bursts.

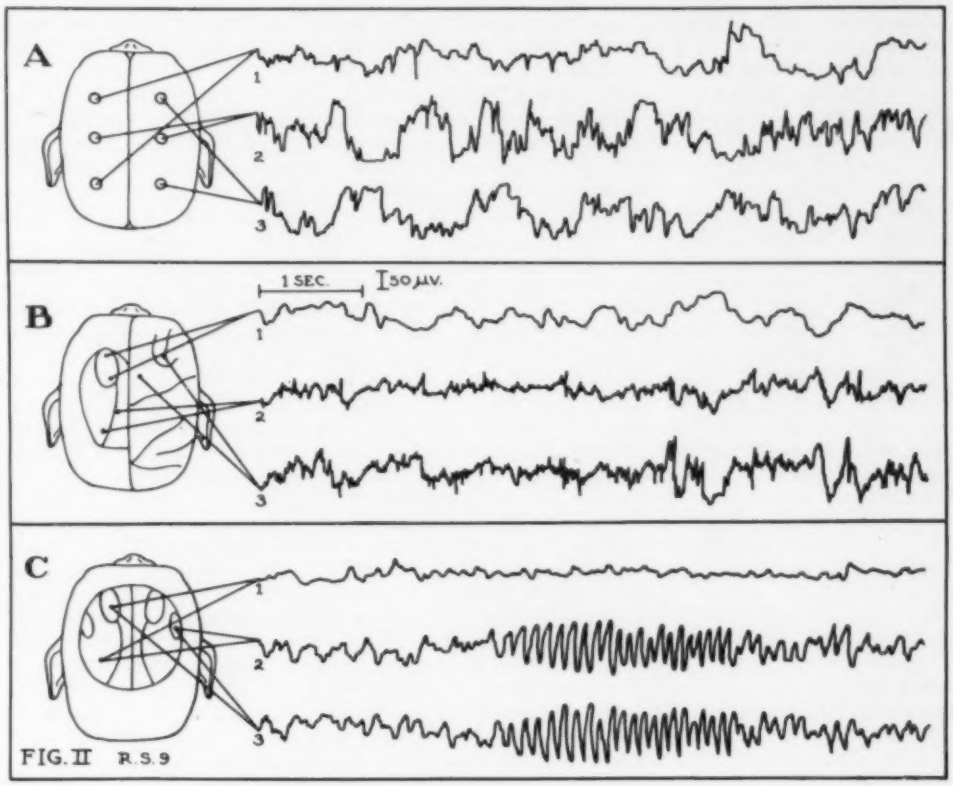

FIG. II R.S.9

From the thalamus potentials were recorded which were of lower amplitude. The rate was faster than that of caudate or putamen, its pattern more irregular. There were at times both fast and medium-slow components such as appear in EEGs from cortex.

At autopsy the brain was cut in frontal slices after hardening in formalin. The points upon which the electrodes had been placed were verified. A small bit of cortical tissue near the left insula was all that remained of cortical gray matter.

Summary: Rhythmic potential changes were obtained from both sides of the remaining tissue of a monkey which had been decorticate for four days and hemidecorticate for a year. These EEGs, like those of cerebral cortex, had a rate and amplitude characteristic for the area under investigation, but the pattern from basal ganglia differed markedly from that of cortex. The most striking characteristic of the former was spontaneous bursts of spikes appearing at irregular intervals. These were never obtained from thalamus or other subcortical structures.

Expt. 2 (R.S. 9), Dec. 14, 1942: This animal, weighing 5.4 kg., had had its left cerebral hemisphere removed on Nov. 23, 1942. On Dec. 14, 1942, it was anesthetized under Dial and records were taken first from the left and right sides of the skull. Fig. 2A shows such records which are characteristic for normal sleep or anesthesia except that the record from the left side is of lower amplitude than that from the right. This latter merely indicates

that it was a greater distance from the excitable tissue to the left side of the skull, since the left hemisphere had been removed.

Figure 2B is part of a record taken from leads placed directly on the tissue which remained on the left. As verified at autopsy two leads (Fig. 2A, 1) were on the caudate and putamen, two (2) were on thalamus, and two (3) remained on the right cortex. It can readily be seen that none of the three areas produced a pattern of EEG which was like that of any other area but that the records from thalamus and cortex are similar and at times synchronous in rate and pattern. From caudate and putamen potential changes were once more obtained which were of low amplitude and fairly regular at a rate of 6 to 8 per sec., without any trace of the rapid component found in electrocorticograms and records from the thalamus.

In this experiment records were taken from 9 a.m. to 1:30 p.m. from left basal ganglia, while the right cortex remained intact, in an unsuccessful effort to obtain the spontaneous rhythmic bursts of activity seen in the record of the previous animal. The right cortex was then removed. As soon as the electrodes were replaced on the same spots on the left side, spontaneous bursts of activity appeared from caudate and putamen and were present throughout the remaining period of the experiment. They were also obtained from the basal ganglia of the right as shown in Fig. 2C.

At autopsy there was no remaining cerebral cortical tissue, except a small bit about 4 mm. in width just rostral to the optic chiasm in the midline.

Summary: In this animal when the left hemisphere was absent, but the right intact, independent rhythms were recorded simultaneously from the left basal ganglia, the left side of the thalamus and the right cortex. These remained consistently typical for each area and differed from each other over a period of 5 hours. During this interval no spontaneous bursts of spike activity appeared in the left basal ganglia but when the right cortex was removed, the record from the left basal ganglia, and from caudate and putamen on the right acquired spontaneous bursts of spike-like hyperactivity such as were seen in the decorticate preparation of Expt. 1. Between bursts the character of the activity from the left basal ganglia was apparently unaltered by the right hemispherectomy.

Expt. 3 (EEG, 14), Jan. 8, 1943: Under Dial anesthesia the cerebral cortex of this normal macaque (weight 4.3 kg.) was exposed bilaterally and normal EEG records obtained from both hemispheres. Following this, area 6 of the left side was gently excavated and electrodes placed on the exposed caudate nucleus. Figure 3A shows the type of record obtained from the left side at this time. Record A1, is from caudate, A2, from area 4 of the cortex about 5 mm. from the excavation, and A3, from the postcentral cortex just across the central sulcus from area 4. The excavation of area 6 apparently produced excitation of area 4, but not of the postcentral region for the large slow waves seen in A2 were not present preceding the removal of area 6, but persisted following this operation until the hemisphere was removed. It is to be noted that, in these records, although caudate potentials were not synchronous with either of the two cortical areas, the caudated record differed markedly from that in the decorticate preparation as shown in Fig. 3C.

Figure 3B is characteristic of records which followed removal of the left cerebral cortex. This record from the left caudate still resembles that of 3A and not that of the same nucleus in 3C. Again, as in A, cortex, caudate and thalamus each presented a different pattern.

Next, after removal of the right hemisphere changes such as were found in Expts. 1 and 2 appeared. Spontaneous bursts of spike potentials became frequent from the basal ganglia of both sides. Figure 3C shows two such bursts, one from left and one from right caudate which are not, however, simultaneous. Neither of these bursts was transmitted to the thalamus. However, occasionally during such bursts a faint trace of the same pattern appeared in the thalamic records, probably due to spread of impulse.

During the remainder of the experiment various lesions of areas surrounding the basal ganglia were made in an attempt to affect the pattern of the record from the basal ganglia. Practically all of the thalamus was removed piecemeal without affecting the bursts. Next the hypothalamus was approached via the midline. Leads placed on hypothalamic tissue in various places at no time recorded any marked pattern in which amplitude and rate could be measured. But excavations here promptly diminished the activity in the EEG from basal ganglia. Since there was then some respiratory difficulty it was felt that these last results were equivocal and conclusions as to the effect of hypothalamus were deferred until the next experiment.

Autopsy findings verified the extent and site of both the lesions and electrodes.

Summary: As in the preceding experiment, hemidecortication, permitted the taking of records from basal ganglia and thalamus. Simultaneous independent rhythms from cortex, caudate and thalamus were obtained under these circumstances, but these became altered when all cortical tissue was removed. The spontaneous bursts of high amplitude spikes were then characteristic of the basal ganglia. Removal of most of the thalamic tissue did not affect these bursts, but ablation of the hypothalamus at once diminished the potentials in all areas until no true rhythmic potentials could be obtained. During the hypothalamus ablation (which followed all other procedures), however, the condition of the animal was not satisfactory.

Since the above three experiments had all shown that the basal ganglia and thalamic

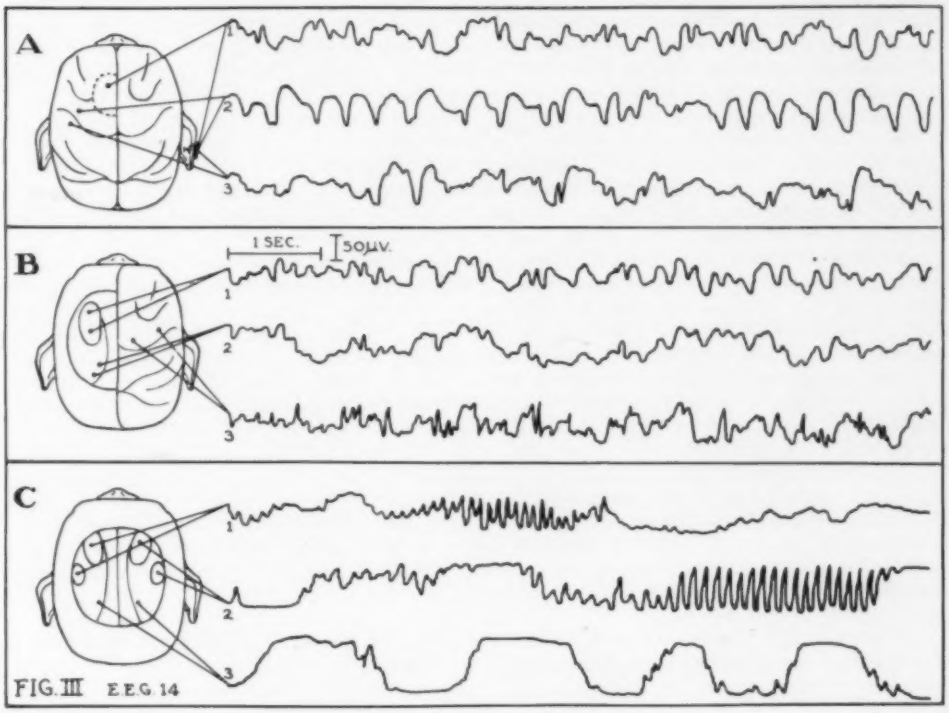

FIG. III E.E.G. 14

nuclei possessed EEGs which existed after total decortication, but that these patterns were altered by the presence of cortical tissue, the next two experiments were planned for further analysis of the cortico-subcortical interrelations.

Expt. 4 (EEG 15), Jan. 20, 1943: A normal monkey, weighing 2.7 kg., was anesthetized and both cerebral hemispheres exposed. Two pairs of bipolar electrodes were then placed on the right cortex, one on pre- and the other on postcentral area and records were obtained from this normal cortex. These leads were then kept in place throughout the remainder of the experiment. The following procedures were carried out:

(i) The left hemisphere was extirpated. There followed a transient disturbance of pattern in the precentral right cortex. It was characterized by large, slow, rounded waves which are indicative of injury. There was no such change in the postcentral area.

(ii) Removal of the left caudate nucleus by suction reproduced these slow waves in the precentral area and they remained there for the duration of the experiment, thus making the character of pre- and postcentral potentials quite different throughout the rest of the procedure.

(iii) Removal of the left putamen by suction caused no further change.

(iv) The falx was next removed after ligation of the longitudinal sinus and the right caudate sucked out from beneath the cortical tissue. The pattern of the EEG was then unchanged except for a slight diminution of amplitude. At this time records from thalamus and postcentral cortex were synchronous and similar in pattern.

(v) The left thalamus and then all of the thalamus was sucked out. Again, amplitude decreased. Furthermore, the postcentral pattern became much less regular both in rate and shape of the waves. At times no true rhythm could be made out, at others there were intervals of many seconds in which irregular waves of varying size would appear.

(vi) Finally, by suction, a large part of the hypothalamus was excavated. This was followed by a marked drop in both amplitude and rate and the pattern became less definite and more irregular in both sites. At times a rapid 9–12 per sec. wave appeared; at others there were only low and faint oscillations.

The hypothalamic extirpations were made piecemeal in four steps. The change in character of the potentials was gradual and increased following each ablation. The difference between the final record and that with intact hypothalamus was marked. Since there had been some respiratory disturbance associated with these procedures it was thought that a resultant anoxia might have affected the cortex. However, these disturbances of respiration were slight, consisting only of an alteration of rate, or an interruption of respiration for the space of one or two breaths. An EEG made one hour after the final operative procedure showed no recovery of EEG, although the animal was still in excellent condition.

At autopsy the lesions were as follows: the left caudate and almost all the head of the right caudate had been destroyed; about one half of the left putamen was absent; virtually all of both hypothalamus and thalamus had been removed.

Summary: Removal of the left hemisphere was followed by the appearance of large, slow waves in right precentral cortex but not in the postcentral region. They were transient. Removal of the left caudate reproduced these waves in right precentral cortex. Ablations of left putamen and right caudate had no further effect on EEGs. But extirpation of the thalamus caused the amplitude to diminish in both cortical areas and further, caused an alteration in the character of the waves, most marked in the postcentral region. Here the rate became slower and the pattern more irregular. Subsequent lesions in the hypothalamus greatly altered the character of the EEG. Amplitude became low and the entire pattern uneven and irregular.

Expt. 5 (EEG 13), Feb. 12, 1943: In this experiment a normal monkey, weighing 5.4 kg., was put under anesthesia and the calvarium removed. The left cerebral cortex was then ablated and bipolar leads placed on right pre- and postcentral cortex. Records were made from these two areas throughout the experiment. A third pair of leads was used to record the EKG in order to observe what effect, if any, lesions of the hypothalamus had on heart rate. Respirations were marked on the record and counted at frequent intervals, for the same reason.

From the right precentral area, following removal of the left hemisphere large rounded slow waves were obtained such as appeared after the same procedure in Expt. 4. Again, these waves were present for only about ten minutes. More normal waves then reappeared, which were slightly faster, of lower amplitude and containing both the medium 6–8 per sec. rate and a faster component such as is seen in the normal EEG. During this entire period records from the postcentral gyrus had remained unchanged.

The anterior inferior portion of the hypothalamus was then removed by sucker from just above the chiasm. There followed a rather gradual change, taking place over at least 15 minutes after termination of the procedure, during which interval there was a gradual diminution in amplitude of the waves. At the same time the rate slowed and the pattern began to look much less regular.

The second procedure was to remove caudate and putamen from the left side. There was no appreciable change in the records which, because of the previous hypothalamic extirpation were definitely irregular and far from normal.

The next procedure was to remove the rest of the hypothalamus from above by entering the foramen of Munro with the sucker and removing all gray matter along the sides of the third ventricle. Respiration and heart rate were unaffected by this. The blood in the cerebral arterioles remained of good color and the pulsation of these vessels indicated a good blood pressure. There followed an intensification of the changes recorded above. Again these appeared immediately after operation and progressively increased over a period of about half an hour. The amplitude during this period diminished greatly and the pattern became

so irregular that its structure could hardly be determined. There were occasional bursts of rapid pulsations which, unlike those seen from basal ganglia, were of low amplitude and all of one height and rate. The postcentral region was affected before the precentral by this manipulation.

About an hour after this last procedure a large hole was made in the left thalamus. All activity again decreased greatly. Waves became slow, 2–3 per sec., irregular and without pattern. There was no fast component present. Removal of the right thalamus next caused a further decrease in activity so that practically nothing remained except a background wavering of the record which was without true form.

During all this period the condition of the animal was excellent. There was no indication from either respiration or pulse that any change in blood supply was present which could have affected the EEG.

Discussion

These findings are not wholly new; furthermore, they are what would be expected in the light of present knowledge of the EEG. Nevertheless, from the above five experiments various matters seem to have become clarified.

First, if the normal EEG, as above stated, is the sum of the voltage differences from the entire complex of the central nervous system, then the findings related to purely cortical ablations can be easily explained. The major portion of the entire cellular gray matter lies in the cortex in all primate forms in which cerebral convolutions are more or less complex. This cortical meshwork is directly or indirectly under the influence of all the subcortical nuclei and may therefore be almost homogeneous in respect to its voltage differences. If, then, even relatively large cortical cellular masses are removed it is not surprising that, although local excisions change local responses as in Expts. 4 and 5, the general pattern is unchanged, because the normal afferent and efferent relations with subcortical structures are maintained. In contrast, since the relatively small cellular bulk of the subcortical nuclei affects relatively large cortical areas, disturbances of the subcortical complexes must alter the total EEG.

In the above experiments it is adequately shown that the normal potentials obtained from either cortex, basal ganglia or thalamus are the result of voltage differences in all three sites, since the removal of one may alter the complexes elsewhere. Certain areas affect only certain others, however, and have little or no detectable influence on potentials elsewhere. This is shown most spectacularly in the basal ganglia-cortical relations. Lesions of caudate and putamen altered the EEG from the precentral region but not from the postcentral. In the absence of part, or all of one hemisphere, the EEG obtained from caudate or putamen is characteristic for that nuclear complex, but is entirely changed by subsequent total decortication.

The change following decortication cannot be due to temporary effect such as tissue injury or anoxia for, in Expt. 1, the left caudate and putamen both gave characteristic background voltages and spontaneous bursts of activity one year after the removal of their overlying hemisphere. It is of passing interest that there is evidence of such function because the basal ganglia have been thought to degenerate in the absence of motor cortex.

Although there is no substantial evidence of the spontaneous bursts of

activity from basal ganglia in the literature, there are suggestions of such a phenomenon in two papers. Jung and Kornmüller (5), describing a method of recording isolated subcortical potentials, show, in their illustrations, certain irregularities in the records obtained from the basal ganglia which look like these bursts of excitation. Gerard, Marshall and Saul (3) using an amplifier from an oscillograph and working on auditory stimuli describe "intense high frequency howls" given by basal regions which "waxed and waned in intensity over a period of a few seconds to three minutes probably as individual units become more or less synchronized."

Individual rhythms were obtained from the thalamus which were alike, whether from midline structures or the lateral parts; from the surface or from the depths of the massa intermedia. They differed in rate, amplitude and pattern from simultaneous rhythms recorded from basal ganglia and cortex. These thalamic EEGs were of rather low amplitude, altough not as low as those from basal ganglia. They contained both medium, 8–10 per sec. rhythm and faster components. They resembled more closely the cortical patterns than those of basal ganglia and, at times but not always, they were synchronous in pattern with the EEG from the postcentral cortex. This is in agreement with the findings of Dempsey and Morison (2,9) as is also the observation that injury to thalamus affects cortical areas. The present findings fit perfectly into the concept of Dempsey and Morison of the electrical activity of a thalamocortical relay system with a reverberating circuit within which many units are coordinated at several levels. This has been analyzed much further by these authors with respect to type of activity and localization within the thalamic nuclei.

Both Grinker and Serota (4) and Obrador (10) have reported that the destruction of the hypothalamus in cats abolished the EEG. The acute preparations of Obrador showed no return of this function. Grinker and Serota report also in acute preparations, that the rhythmic potentials returned after some minutes. A similar diminution in amplitude appeared temporarily in the present preparations following partial destruction of the hypothalamus. Several small lesions made following each other served to summate so that after the last, there was a much greater deficit than that which followed preceding extirpations. The same thing was true with regard to the thalamus, successive partial destruction of thalamic areas was followed at each procedure by diminution of amplitude of EEG and by a loss of definition within its pattern. Only when both thalamus and hypothalamus were practically totally destroyed did the EEG disappear and not reappear even after an hour during which the general condition of the animal remained excellent.

There is one finding for which there is as yet no explanation, *i.e.*, following lesions of both thalamus and hypothalamus there was, for a period of from 15 min. to one-half hour after termination of all operative procedures, a progressive diminution of the amplitude and pattern of the EEG from the cortex. It is to be inferred that in some way the reverberating circuit through

cortical and subcortical areas takes this measurable period of time to adjust. In contrast, lesions of either cortex or basal ganglia seemed to produce maximal effect immediately at termination of the operation.

There is evidence, from chronic preparations, that similar interdependence between nuclear complexes exists. The effect of lesions of basal ganglia on EEG of chronic monkeys has already been demonstrated, results of experiments concerning thalamus and hypothalamus will be published shortly.

Summary

1. Electrical potentials have been recorded from cortex and subcortical nuclei in decorticate and hemidecorticate monkeys.

2. Simultaneous EEGs made from these areas may be independent of one another and the patterns from cortex, basal ganglia, thalamus and hypothalamus are characteristic for each specific area.

3. Each cellular complex, however, influences the other complexes. In particular lesions of the sub-cortical nuclear complexes affect cortical potentials.

4. The EEG obtained from basal ganglia of a hemidecorticate preparation shows low-voltage eight-per-second background potentials. Only when all of the cerebral cortex is removed do spontaneous bursts of high-voltage activity appear.

5. The pattern obtained from thalamus has a medium-rate component, as in the cortex. At times records of thalamus and postcentral cortex are synchronous. Lesions of thalamus alter the pattern of cortical EEGs in general but most markedly in the postcentral areas.

6. There is little activity within the normal hypothalamus but its ablation profoundly alters cortical EEGs.

8. Partial ablation of thalamus or hypothalamus temporarily alters cortical EEGs, but only when both thalamus and hypothalamus are completely extirpated are these cortical potentials abolished.

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SPONTANEOUS ELECTRICAL ACTIVITY OF THE THALAMUS AND OTHER FOREBRAIN STRUCTURES

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STIMULATION of thalamic regions associated with the internal medullary lamina has given rise to alterations in the electrocorticogram which appear to be related to the spontaneous intermittent bursts of 5–10 cycle activity characteristic of the nembutalized cat (11). On the other hand, stimulations more laterally in N. ventralis lateralis pars externa (6) or ventralis posterior of Magoun and McKinley (8) and the geniculate bodies produce changes which can be shown to bear relation to other more continuous forms of cortical activity (1) in localized cortical regions receiving their projections.

The present study was undertaken in order to find out whether these two different thalamic regions exhibited characteristic differences in their spontaneous activity.

Though specifically directed to the preceding question, the experiments also yielded data regarding the activity of other structures which, though limited in scope, appear to be worth reporting in view of the incomplete nature of existing information.

The most complete surveys of the spontaneous electrical activity of the basal prosencephalon are those of Gerard, Marshall and Saul (3) and Morea (10), but the general utility of the former is somewhat limited by the fact that the records were made largely in the form of verbal descriptions of the sounds emanating from a loudspeaker. In the present study, the admittedly greater differentiation allowed by their procedure has been sacrificed for the greater permanence and transmittability of the graphic method.

METHODS

Cats anesthetized with nembutal were used, an effort being made to adjust the anesthesia to a point at which well defined intermittent bursts of 5–10 cycles were recorded from the cortex. The exploring electrodes consisted of two enameled stainless steel wires separated at their bared tips by a distance of 0.3 to 6.0 mm. These were oriented in the brain by means of the stereotactic instrument previously described (12). In most of the experiments other bipolar silver electrodes were placed on representative cortical areas in order to obtain data for correlation with activity in deeper structures. In other experiments various cortical ablations were made. The recording instrument consisted of a multichannel Grass inkwriter.

At the termination of each experiment the brain was removed and fixed in formalin for sectioning and staining by the method of Marshall (9). Direct positive enlargements were made from the sections and the points of recording identified on the prints.

In order to obtain a graphic representation of the distribution which would appeal more immediately to the eye, the following method was employed.

Representative cross sections were projected at 30 times magnification and sketches of important landmarks and the needle tracks were made. Typical excerpts of the records were then mounted upon the sketch with reference to the coordinates of the stereotactic

instrument. Photographic negatives were then made of a suitable section and of the mount of the records, the sketch of the section on the latter having been erased. Suitable magnification of the section and reduction of the mount were made such that they could be superimposed to give a final print with a magnification of the section at 10× and a reduction of the record mount to one-third. When using material stained with the Weil method, a negative of the section was masked with a positive of the mount. The final print thus contained a positive of the section and a negative of the electrical activity (*cf.* Fig. 4, 6, and 8). With Nissl material superposition of two positive prints was made by the method of double exposure (Fig. 5 and 7).

Accurate register was obtained in both instances by reference to horizontal and vertical lines scratched on the original slide at some distance from the field of interest and included in the tracing used for the record mount.

Results

Thalamus. In spite of the great difference in conditions encountered deep within the thalamus from those in the cortex, records from the two organs showed strikingly similar features. The intermittent "burst" activity, re-

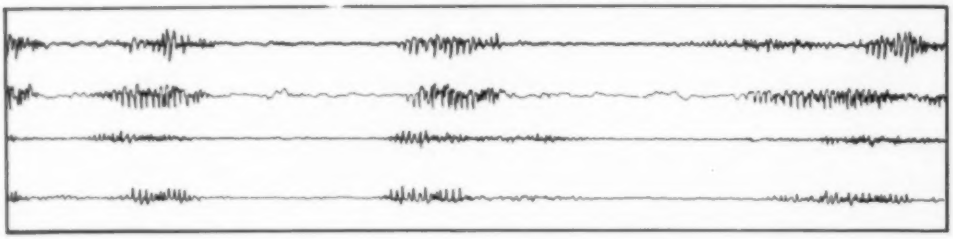

Fig. 1. Synchrony of burst activity in thalamus and various parts of cortex. Record begins just before the end of a burst. Upper tracing from point in thalamus similar to that for tracing 6 (from top down) in track 1 (most medial) Fig. 5 (but not the same experiment). Second tracing: anterior sigmoid gyrus; third tracing: arm sensory area; lowest tracing: middle suprasylvian gyrus. The record was taken at a paper speed of 15 mm. per sec. and reduced to ⅓.

ferred to above as characteristic of the cortex of cats under nembutal, occurred in similar form in specific parts of the thalamus. In many cases the frequency of occurrence of the bursts and that of the waves within them, though of similar general character, were not identical with those emanating from any particular cortical position. In others striking similarity with one

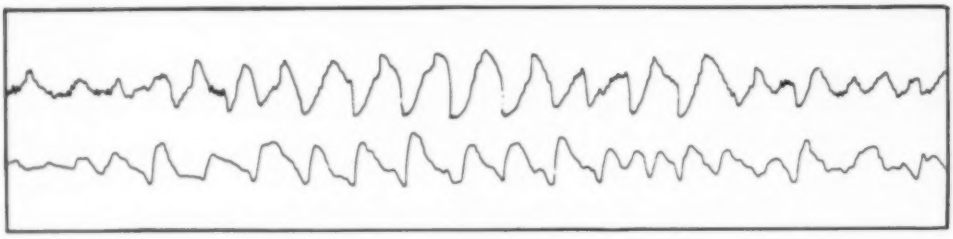

Fig. 2. Approximate wave to wave correspondence between thalamus and cortex. Upper tracing: same as tracing 6, track 1, Fig. 5. Lower tracing anterior sigmoid gyrus. Paper speed 60 mm. per sec. (reduced to ⅓).

or more of the surface positions was obtained (Fig. 1). In only a few instances, however, was a one to one correlation of individual waves possible, the most striking case occurring in a preparation rather deeply anesthetized and showing practically no interburst activity (Fig. 2).

Intermittent bursts of this sort were recorded from a rather wide area in the thalamus, especially in medial and intralaminar regions. Figures 4–8 illustrate the distribution in a typical experiment. In most of the experiments some bursts were recorded laterally and dorsally in the thalamus (*cf.* Fig. 5, trace 1 and 2, track 3; and Fig. 6, trace 1, track 2 and 3; also the dorsal

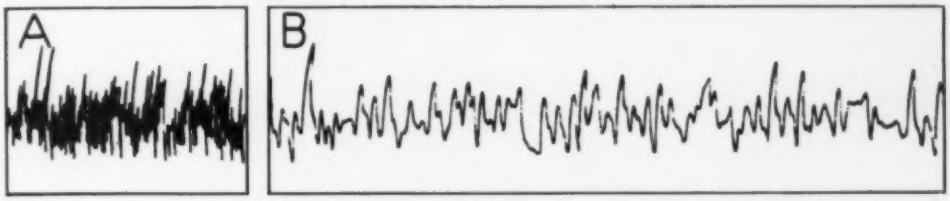

FIG. 3. Spontaneous activity of point similar to 6th tracing, track 5, Fig. 6. At two different paper speeds: A, 15 mm. per sec.; B, 60 mm. per sec.

area in Fig. 7 which was not explored in the case illustrated and may be attributed to lateralis posterior or pulvinar). In most of these, however, the highest voltage and greatest frequency of occurrence were found more medially. Coordination with the cortical activity was also greater in the medial areas. Burst activity has never been encountered in pars externa or the medial and lateral geniculate bodies. Fortunately one does not have to rely wholly upon histological checks for the determination of the recording point in these relay nuclei, since they are the seat of distinctive potentials evoked by stimulation of the appropriate sensory receptor (8). As Dempsey and Morison (1, Fig. 5) have shown, burst potentials did not occur in areas where sensory responses to radial or sciatic nerve stimulation were recorded. In the present series of experiments this point was repeatedly checked and extended to include areas responsive to stimulation by light or sound.

Occasionally bursts appeared in the vicinity of ventralis medialis (*cf.* Fig. 6, trace 4, track 2) which might be attributed therefore to a relay nucleus since this area has been shown (8) to receive the trigeminal lemniscus. Since this would be the only relay nucleus exhibiting such activity in these experimental conditions, it seems more desirable to attribute the activity to the immediately adjacent centralis lateralis or center median.

In some experiments, ventralis lateralis appeared to be the site of some bursts; in others they were absent though present in the more medial areas. The interpretation of this finding is obscure.

In preparations which exhibited little or no burst activity in the cortex, correspondingly poor results were obtained from the thalamus. Particularly instructive were cases in which the activity disappeared from the cortex, having once been present or, conversely, developed after having been absent;

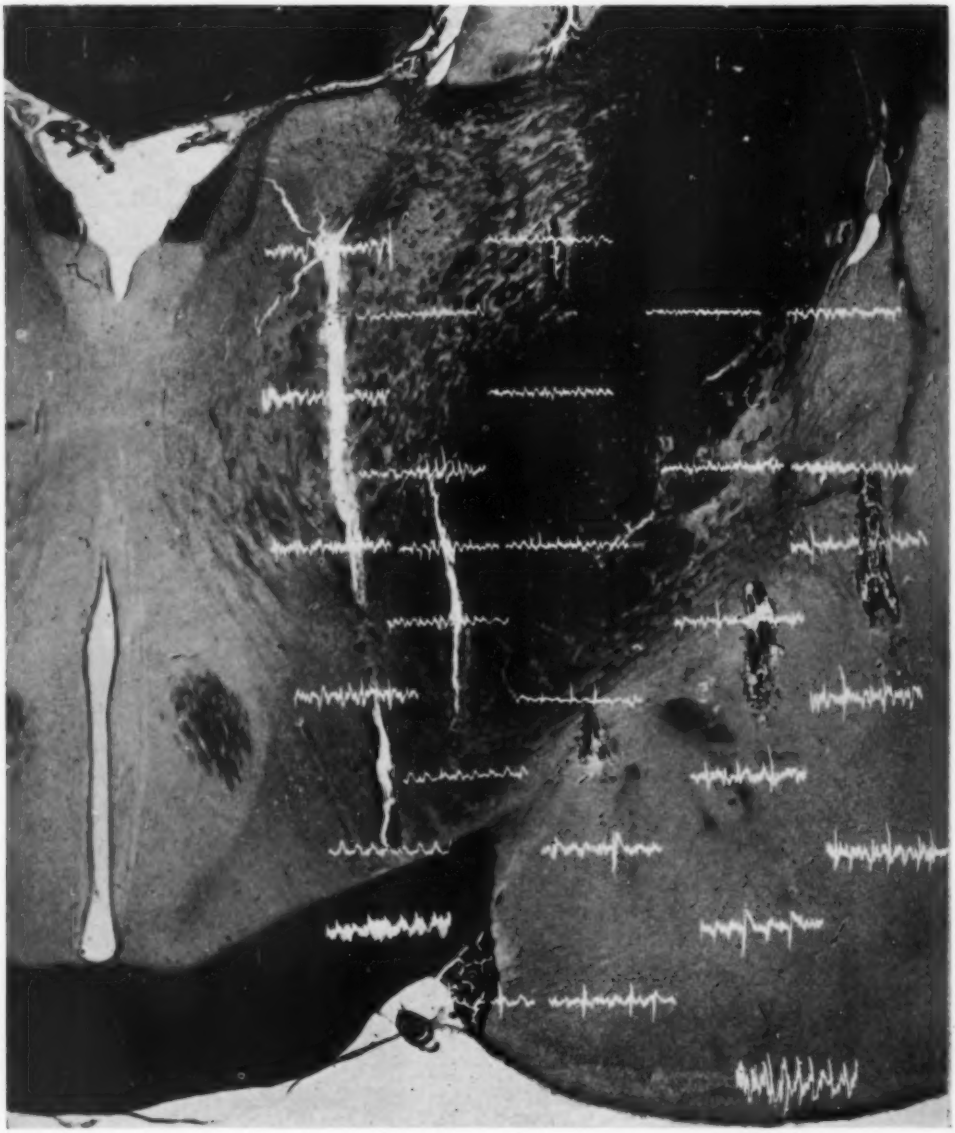

FIG. 4

FIG. 4–8. Distribution of spontaneous electrical activity of thalamus and other basal areas in a single representative experiment. For technique of constructing figures consult *methods*. The electrical records were taken at 15 mm. per sec. and reduced to ⅓. The brain sections were enlarged 10×.

Typical bursts were selected from areas showing intermittent activity. All other records are representative of the continuous activity present. The vertical markers to the left of some tracings in track 1, Fig. 5, indicate 50 μV. All records in Figure 4 and the first three in Fig. 5 were taken with amplification as in tracing 3; all subsequent to tracing 6 as in tracing 6.

There was a slight displacement of the needle tracks from the plane of section in some instances. This was so slight as to be negligible except for a few points deep in the amygdala and pyriform lobe in which the records may have been taken from points as much as 4–500μ rostral to the points represented.

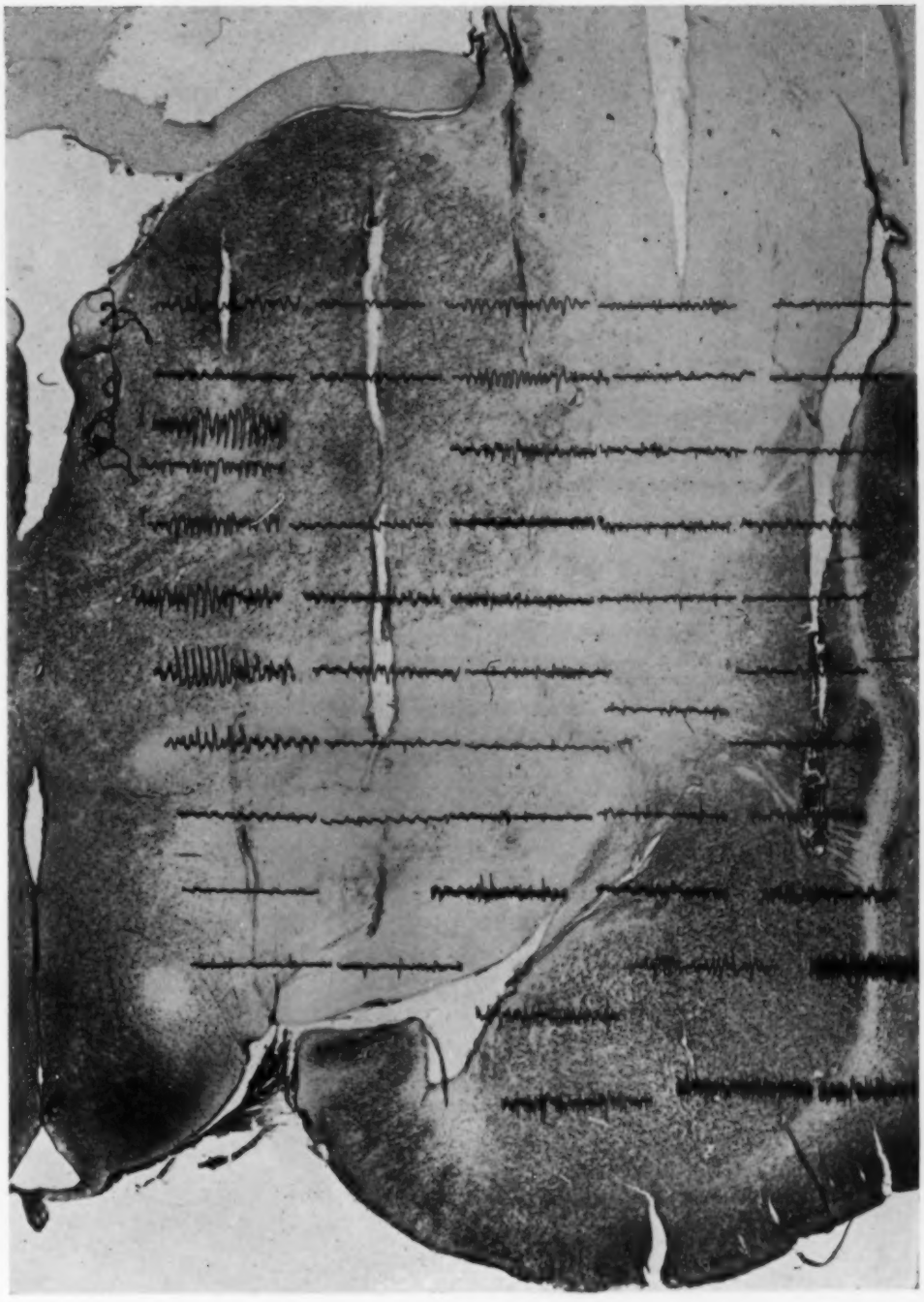

FIG. 5

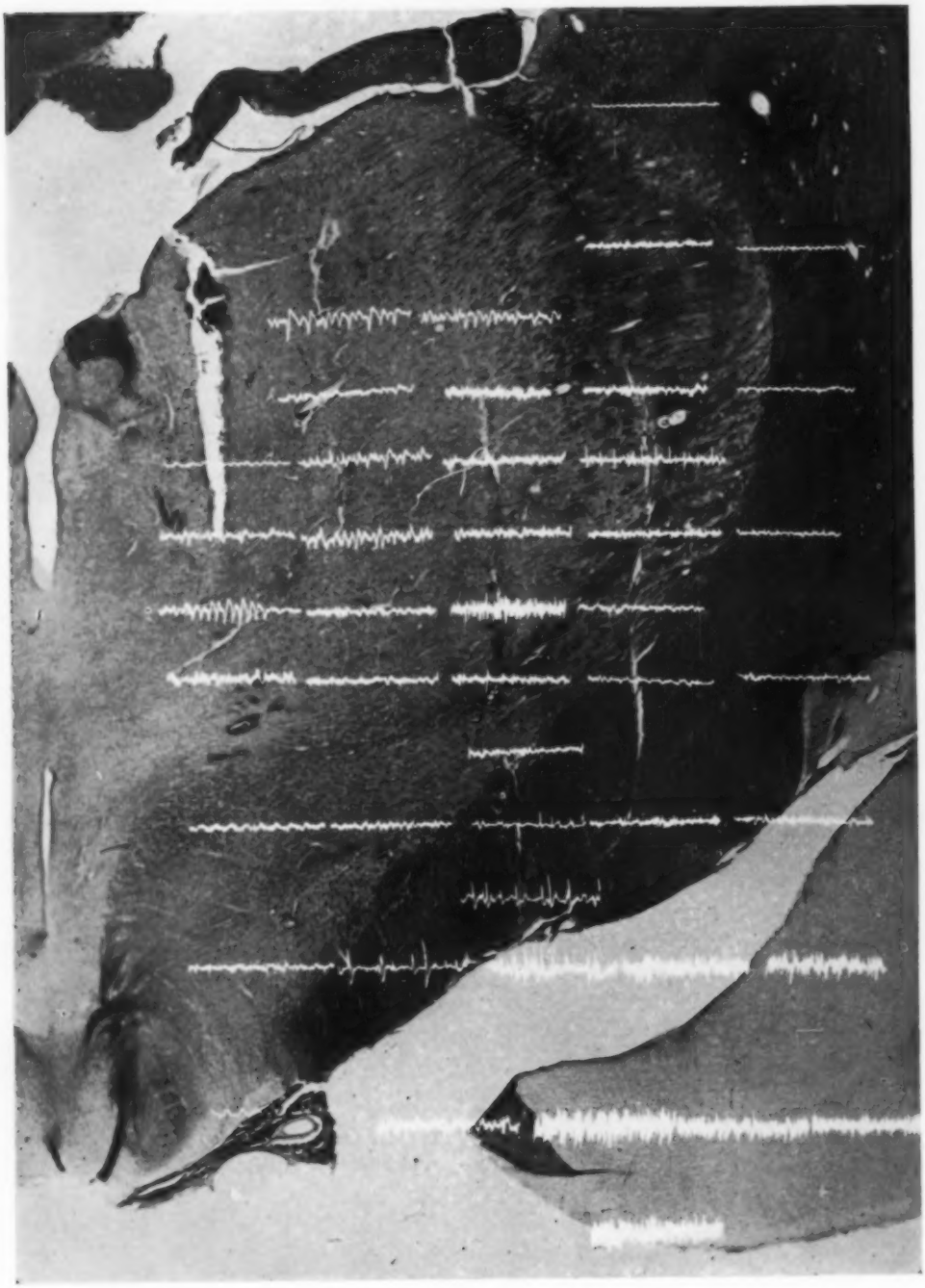

FIG. 6

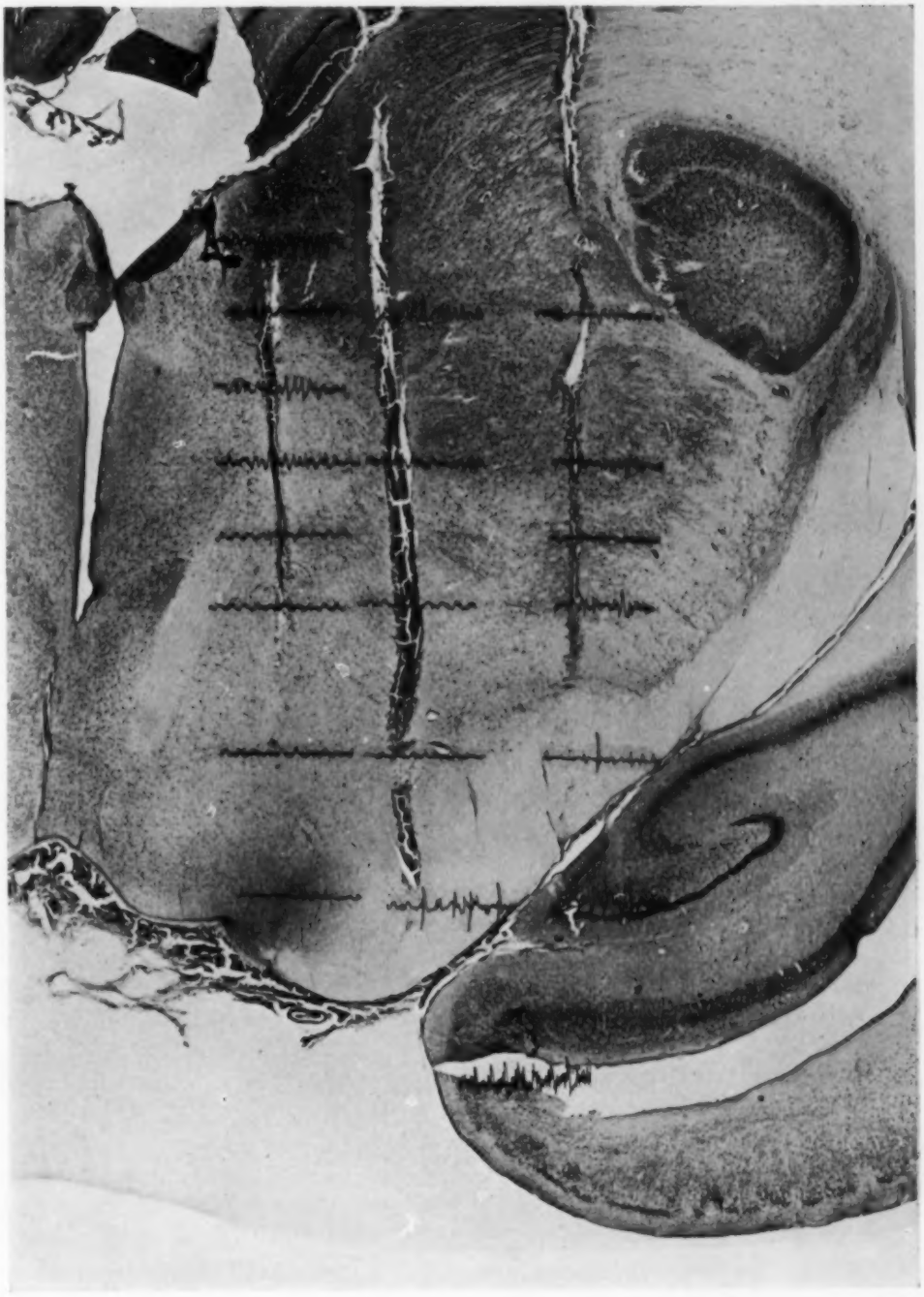

FIG. 7

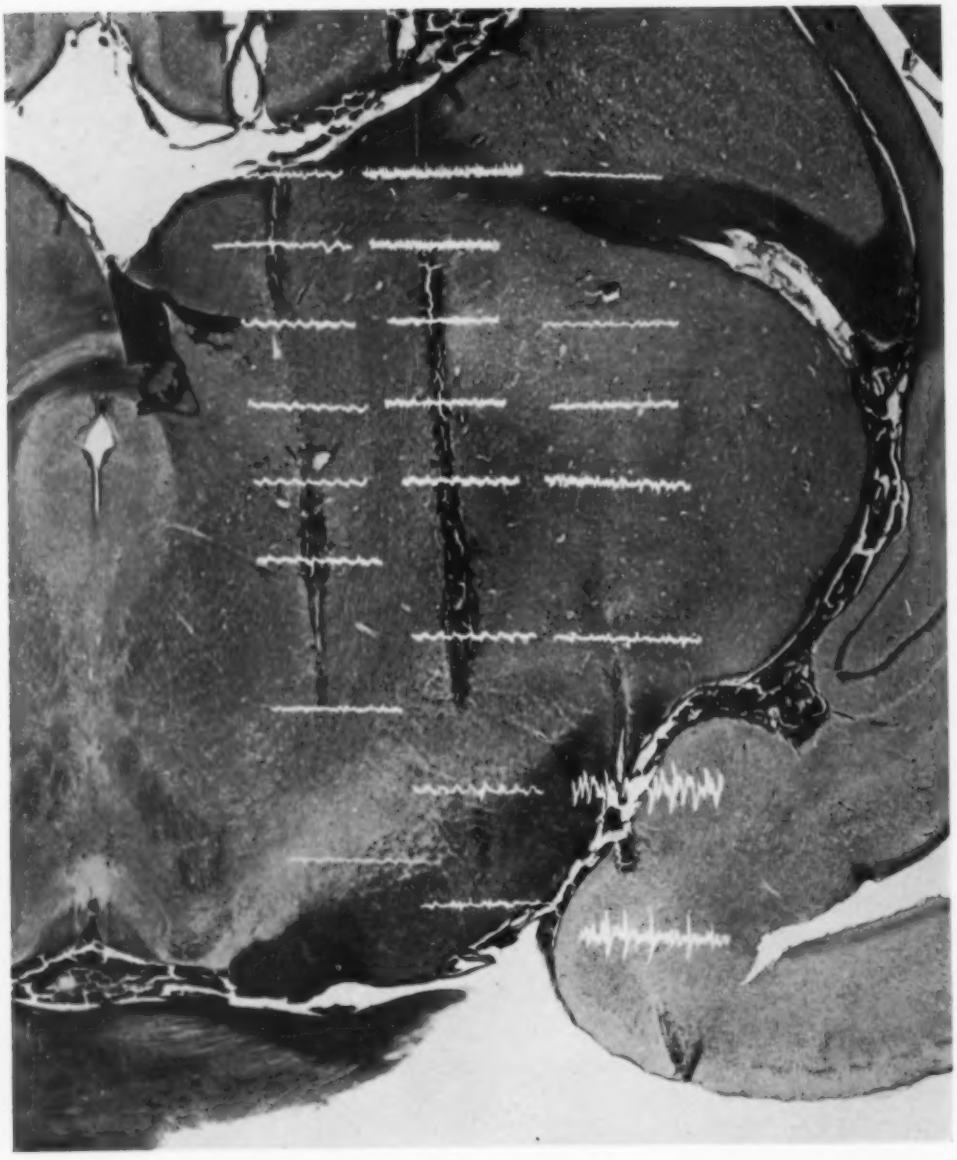

FIG. 8

the changes in the thalamus paralleled those in the cortex. On the other hand, excellent bursts have been recorded in the thalamus of preparations with large homolateral cortical defects. In one instance in which all the neopallium of one side was removed, a complete map of the burst activity in the thalamus was made which coincided closely with that in intact animals.

In another case, besides unilateral removal of the cortex, an incision was made separating the two hemispheres as far back as the mammillary bodies. Celloidin sections revealed that a few fibers of the supramammillary decussation and about one-half of the posterior commissure were spared. Good bursts were also recorded from this preparation for a period of about one-half hour.

On the basis of such experiments it is difficult to say whether the spontaneous bursts are a property solely of the thalamus or depend upon the presence of the cortex. Either the early presence of activity after the extensive operative procedure or its subsequent decline might be due to unspecific traumatic factors. Further work in chronic preparations may serve to resolve such questions.

Activity in the relay nuclei (pars externa and geniculates) in these experiments was usually confined to continuous rapid fine spikes of somewhat higher voltage than in surrounding areas (*cf.* tracing 4 and 5 in track 3, Fig. 6, etc.). Occasionally, when the anesthesia was light, there emerged more organized patterns very similar to those recorded in sensory cortex under proper conditions (*cf.* Fig. 11 in the paper by Dempsey and Morison, 1). Decortication sharply reduced activity in these nuclei (2) in contradistinction to its apparent lack of effect on the bursts recorded elsewhere.

Hippocampus fornix system. High voltage spikes of fairly rapid frequency were usually encountered when the electrodes penetrated the hippocampus or fornix dorsal to the thalamus and tended to disappear over a period of several minutes. No specific attention was directed to them as this system has been studied intensively by others (13). It may, however, be worth recording that in one decorticate preparation two spontaneous "tonic clonic" episodes entirely similar to that illustrated by Rosenblueth and Cannon (14) as the result of faradic stimulation were observed.

Hypothalamus. Records taken from the posterior hypothalamus and tuber region consisted almost solely of fine irregular rapid potentials without notable peculiarities. The supraoptic region, however, sometimes yielded more definite waves of 10–12 per sec. frequency. These types of activity were similar to those pictured in Fig. 2 of the paper by Hoagland and others (5). As the latter workers point out, the nuclear complexity of the supraoptic region and its environs necessitates caution in assigning a definite source to the potentials encountered. Under the present experimental conditions, moreover, nothing was found to suggest an intimate relation between cortical activity and that of the hypothalamus or of any part of the supraoptic region (4).

Other areas. Spikes of slow and often irregular rhythms upon nondescript more rapid low voltage background were occasionally recorded from lateral

subthalamic areas and in the neighborhood of the globus pallidus, peduncle or possibly the substantia nigra.

Most dramatic results were obtained when the electrodes left the diencephalon and penetrated telencephalic structures beneath or laterally. Owing to the semidetached nature of this part of the brain, which includes the pyriform lobe, amygdala and hippocampus, identification of the exact recording point is difficult, especially in regard to the dorsoventral coordinates. Higher voltage rapid activity (Fig. 3) was always found widely scattered throughout this region both posteriorly where the hippocampus might be responsible and also more rostrally (Fig. 4 and 5) where the amygdala or pyriform lobes were more likely sources. The intensity of this activity declined slowly as the electrodes remained in one position, but was still marked after periods as long as 20 minutes. It thus became a matter of opinion whether the decline was a matter of recovery from injury or, conversely, was due to accumulations of shunting fluid about the electrode tips.

Similar but usually less striking effects were found when the electrodes were in the ventral parts of the putamen or globus pallidus (Fig. 4 and 5). This may, however, merely represent spread from amygdala.

No statement as to the activity of the caudate nucleus is to be made on the basis of these experiments as the proximity of the ventricle makes depth determination of the electrodes very difficult with the technique employed, *i.e.*, the large size of the ventrical at this point may be considerably varied by shifts in spinal fluid, or other temporary distortions may be brought about by the penetrating electrodes without the change being registered on the final section.

Discussion

Principal interest in this study attaches to the distribution of the spontaneous burst activity in the thalamus. This was found to be most intense in regions dorsal and especially medial to the relay nuclei, an arrangement which is consistent with other data (1) which suggest that the latter structures are not primarily related to the intermittent bursts recorded in the cortex. The distribution coincides rather closely, however, with points stimulation of which was followed by an increase in the bursts throughout the neocortex (11).

The active points were dispersed beyond the limits of any single thalamic nucleus but most intense activity was usually found in the intralaminar group. Activity encountered in dorsolateral regions containing nuclei related to "association areas," is in general consistent with the previous finding that association areas exhibit burst activity most intensely (11). Whether or not this activity originates purely in the intralaminar nuclei, such as the centre median or centralis lateralis, and involves more lateral and dorsal regions secondarily is difficult to determine. Such primacy of the intralaminar group is suggested by the usually greater ease of eliciting the "recruiting response" by stimulating these areas, and by the fact that the recorded activity was usually greatest here.

As is well known, the bursts, though tending to occur simultaneously in all cortical areas, by no means always do so. Similarly the present results allow the deduction that the thalamic bursts are not simultaneous in different parts of the thalamus. For example, in the same experiment a given thalamic area might be simultaneous with say the cortical sensory area. A change of a few millimeters in electrode position might result in bursts bearing no relation to the sensory area but, for instance, to the middle suprasylvian gyrus. Frequently no relation to any of the cortical areas concurrently recorded could be made out. The finding of different rhythmic patterns in different parts of the thalamus, especially differences in frequency of incidence of the bursts, though difficult to render in quantitative terms, also supports the idea that specific parts of the thalamus are at least semi-independent in the production of burst activity.

The finding of excellent burst activity in the thalamus deprived of all homolateral neocortical connections and a high proportion of interhemispheric commissural systems is of particular interest. As was pointed out above, these experiments are not conclusive, but they suggest very strongly that such activity does not depend upon the presence of a reverberating corticothalamic circuit. Activity in relay nuclei, on the other hand, is usually severely depressed, though not abolished, by interference with cortical connections. Though further work is necessary to establish the hypothesis, it may be permissible to speculate upon the arrangements underlying the spontaneous bursts. One area in the neighborhood of the centre median may be thought of as having the greatest tendency to produce intermittent burst activity. It also is presumed to have rich connections with other more widely diffused thalamic cell groups associated with but not identical to the nuclei giving rise to "specific" cortical afferents. The latter nuclei have been described by Lorente de Nó (7) as giving rise to "non-specific afferents" of a diffuse sort which fit well the requirements of the system under discussion. These nuclei may be postulated to have a tendency toward spontaneous activity of their own and so account for the lack of synchrony often encountered in divers cortical and thalamic areas. On the other hand, they may under other conditions be relatively easily controlled by the "master" oscillator in or near the center median. The latter supposition accounts for the cases of spontaneous synchrony frequently encountered and especially for the fact that stimulation of this area is most effective in eliciting the "recruiting response" (11) simultaneously throughout the cortex.

Summary

1. The spontaneous activity of subcortical forebrain areas was recorded by means of bipolar electrodes oriented with a stereotactic instrument. Spontaneous bursts of 5–10 per second waves similar to those seen in the cortex were recorded in various thalamic areas (Fig. 4–8), chiefly in those associated with the internal medullary lamina but never in the "relay nuclei." These and other data suggest that several thalamic areas presumably

giving rise to "non-specific cortical afferents" have a tendency to produce spontaneous rhythmic bursts, but that they may be under the additional control of a master area associated especially with the internal medullary lamina.

2. Characteristic spontaneous activity in other subcortical regions was recorded and is briefly noted.

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ACUTE PHYSIOLOGICAL EFFECTS OF GUNSHOT AND OTHER PENETRATING WOUNDS OF THE BRAIN

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IN THE STUDY of experimental cerebral injuries in the dog, the acute physiological effects of gunshot and other penetrating wounds appeared to be of particular interest. These observations are, therefore, reported in detail.

TECHNIQUE

Mongrel dogs weighing between 7 and 15 kg. were used for this study. The experiments were performed under morphine analgesia in quantities of 20 mg. per kg. The blood pressure was recorded from the femoral artery; respirations, by means of a balloon about the thorax. The spinal fluid pressure was recorded from a needle inserted in the cisterna magna and attached to a 1 mm. bore water-manometer. Six-tenths cc. of cerebrospinal fluid was required to fill the system to starting pressure. Difficulties were encountered in recording the intracranial pressure at the instant of a bullet's penetration. Various systems were employed. Only a qualitative change in pressure could be recorded. Bullets of varying velocity and size produced the injuries. These were the pellet, the bullet of the 22 BB revolver which weighed 20 grains and had a speed of 780 ft. per sec. and the bullet of the 22 short rifle which weighed 40 grains and had a speed of 970 ft. per sec. In a total of 24 animals, 3 were injured with pellets from an air revolver, 16 with a 22 BB revolver and 5 with a 22 short rifle. A mechanical drill was used to obtain a penetrating injury of minimal velocity and this was done in two instances. As a rule, the animals were injured with the soft tissues intact and the cranial cavity closed. In a number of instances, the wounds were made after disturbance of the closed cavity hydrodynamics by opening the cistern to expose the medulla; suboccipital craniectomy to expose the cerebellum and brain stem and unilateral or bilateral supratentorial craniectomy to expose one or both hemispheres. Infiltration of 1 per cent procaine hydrochloride was used in these procedures for local anesthesia.

RESULTS

1. *Effects upon blood pressure, respirations, reflexes, conscious state and mortality.* The results of injuries produced by the pellet shot, the 22 BB (revolver), the 22 short (rifle) and penetration of the brain by a mechanical drill could be classified into *profound*, *moderate* and *minimal* physiologic effects as shown in Fig. 1.

Profound. A profound result was produced by 22 rifle injury in every instance. Among 7 of 14 experiments with 22 revolver injury, profound effects were also produced. No such effects were noted with the pellet shot. The profound effect was uniformly characterized by respiratory paralysis, abolition of lid and corneal reflexes, a marked hypertension and death of the animal (Fig. 2). Coma* was immediate. Extensor spasms were absent in most instances. The hypertension did not occur in those experiments in which the medulla was directly injured (Fig. 3). It also failed to appear after adequate

* Coma: A state of absolute unconsciousness as judged by the absence of any psychologically understandable response to external stimuli or inner need. (British Research Council, Head Injury Committee, 1941).

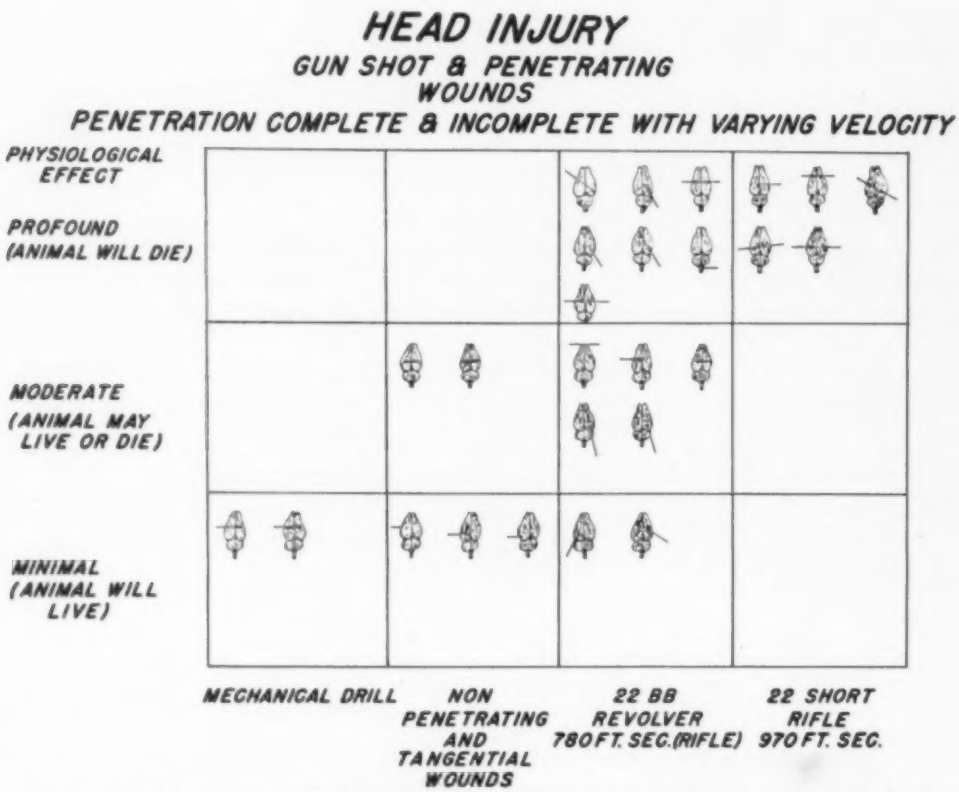
HEAD INJURY
GUN SHOT & PENETRATING WOUNDS
PENETRATION COMPLETE & INCOMPLETE WITH VARYING VELOCITY
PHYSIOLOGICAL EFFECT
PROFOUND (ANIMAL WILL DIE)
MODERATE (ANIMAL MAY LIVE OR DIE)
MINIMAL (ANIMAL WILL LIVE)
MECHANICAL DRILL
NON PENETRATING AND TANGENTIAL WOUNDS
22 BB REVOLVER 780 FT. SEC. (RIFLE)
22 SHORT RIFLE 970 FT. SEC.

FIG. 1. Showing the distribution of physiological effect in relation to the sustained injury. The bullet of the 22 BB revolver weighed 20 grains and that of the 22 short rifle, 40 grains.

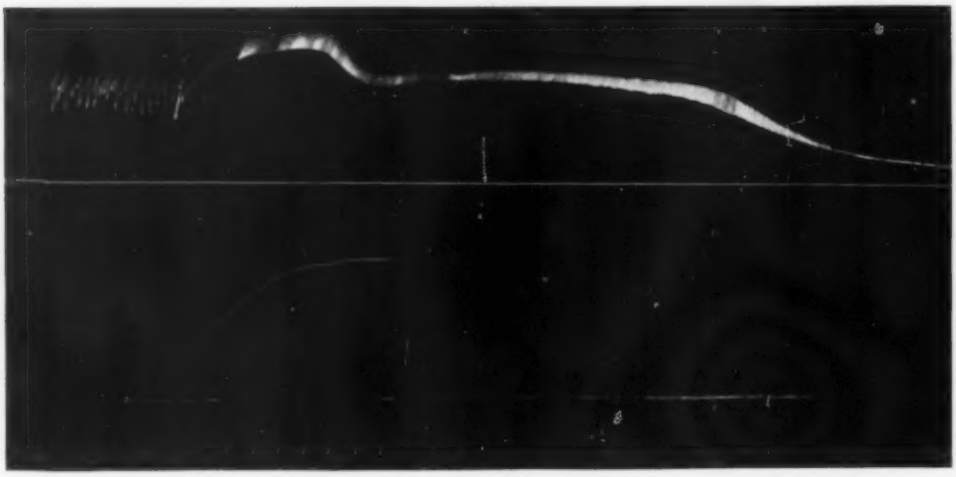

FIG. 2. Morphine analgesia. Typical curve following a 22 short rifle injury. The bullet entered the anterior fossa of the skull in front of the sella. Profound effect was produced. There were petechial hemorrhages in the pons.

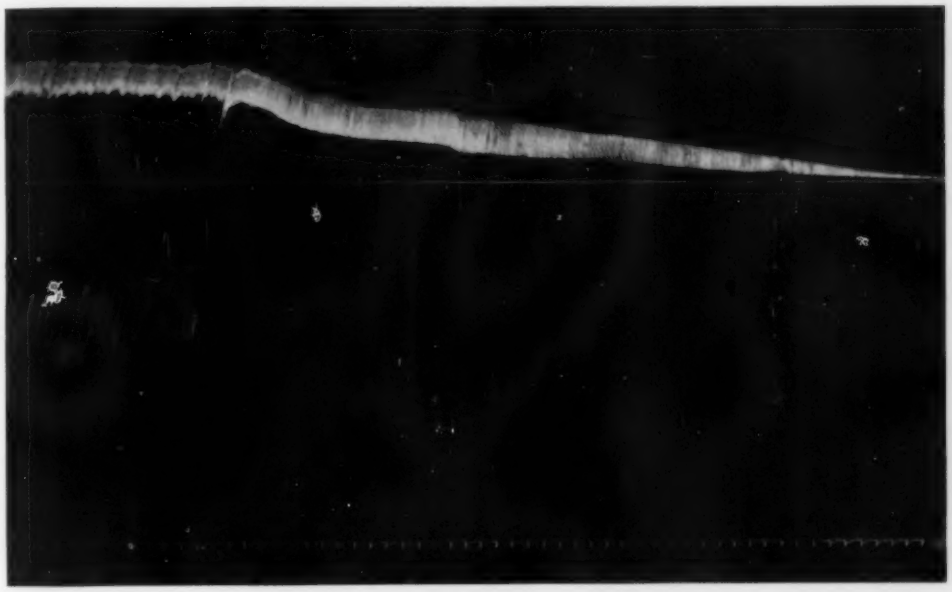

FIG. 3. Morphine analgesia. 22 short rifle injury, the bullet entering the medulla. A profound effect was produced without elevation of the blood pressure.

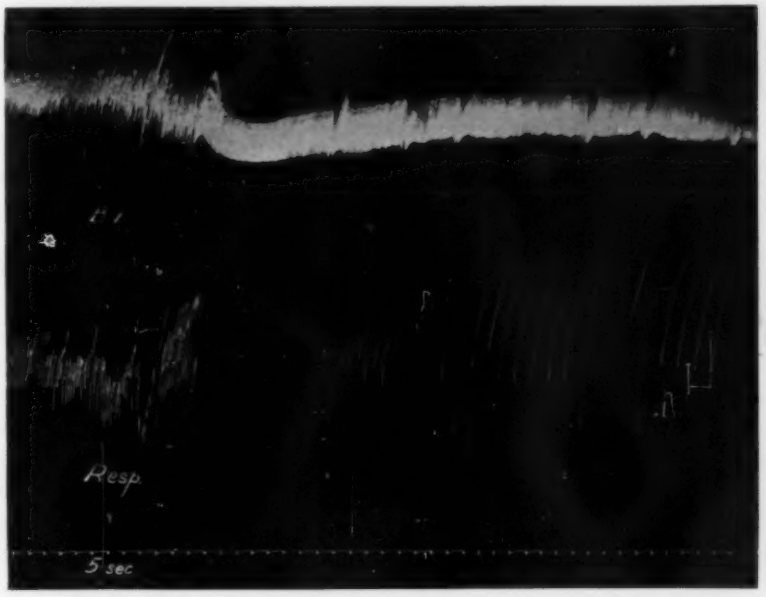

FIG. 4. Morphine analgesia. 22 short rifle injury following bilateral decompression exposing both cerebral hemispheres. No rise in blood pressure. Reflexes lost for 2 minutes and 30 seconds. Respirations lost for 40 seconds. The animal remained unconscious throughout. With the cranial cavity closed, this type of injury would be fatal with a pattern as illustrated in Figure 2.

decompression before injury by shooting (Fig. 4). In the latter group, the respiratory function was spared in the acute phase of the experiment.

The pathological damage, under these circumstances, was of severe grade. A common finding was the presence of petechial hemorrhages. These were of varying size and number, occurring adjacent to the site of penetration; the pons and frequently in the medulla and upper cervical spinal cord.

Moderate. A moderate effect resulted from injuries produced by the 22 BB revolver in 7 instances out of 14. The animals in this group either died or survived the acute experiment. Temporary arrest of respirations occurred for periods which varied from five to thirty seconds. Lost palpebral reflexes

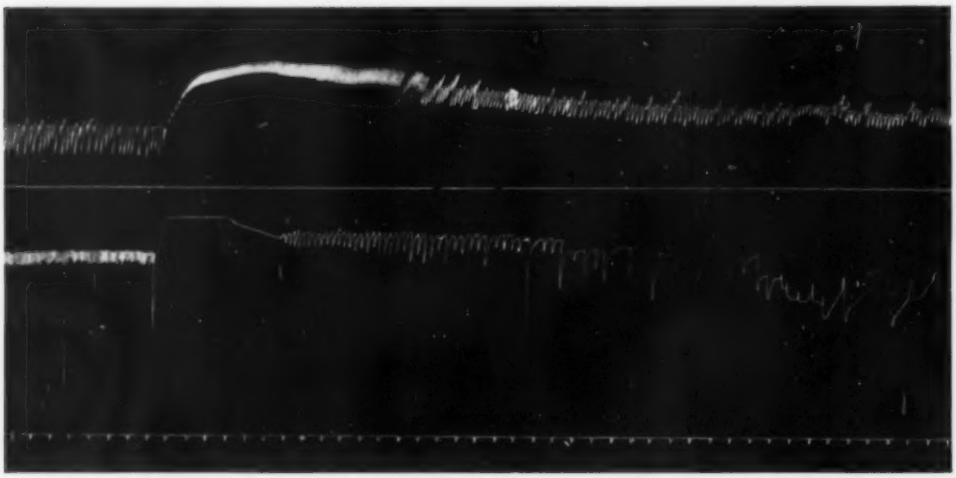

FIG. 5. Morphine analgesia. Injured with a 22 revolver, bullet lodged in the brain. Cessation of respirations for 35 seconds but reflexes were present throughout. The dog was unconscious. The lid reflexes may not serve as a criterion for accurately determining consciousness. The spinal fluid was bloody with a pressure of 115 mms. Type of injury, moderate.

returned at periods of from 3 to 145 seconds. A rise in blood pressure with tachycardia was consistently observed (Fig. 5). In some experiments there was a dissociation of conscious state and the palpebral reflexes; that is, some unconscious animals had preserved reflexes.

The gross pathologic damage was less severe than in the preceding group. The bullet usually lodged in the cerebral substance. Distant lesions were less frequent.

Minimal. A minimal effect followed trauma by the pellet shot in 3 instances; by the 22 revolver in 2 instances out of a total of 14; and by the use of the hand drill. With gunshot injuries producing a minimal effect, there was fracture of bone without penetration or the bullet stopped at the skull without injury to bone. By the use of a mechanical drill, both bone and brain were penetrated. Members of this group all survived the experiments. Respirations and reflexes were preserved. In some animals the respirations were

stimulated; in others, slowed. Consciousness was maintained. The blood pressure usually remained unchanged (Fig. 6). Pathological examination of the specimens from this group indicated mainly local damage with or without hemorrhage from the site of injury.

2. *Effect upon the intracranial pressure.* A sudden, intense, increased intracranial tension of brief duration was observed to accompany the gunshot injuries of the brain. Evidence of an intense pressure was visualized by exposure of the cisterna magna. Under this condition, at the moment of injury, the cerebellum was expelled into the opening made. A suboccipital craniectomy followed by a supratentorial, gunshot injury was observed to result in

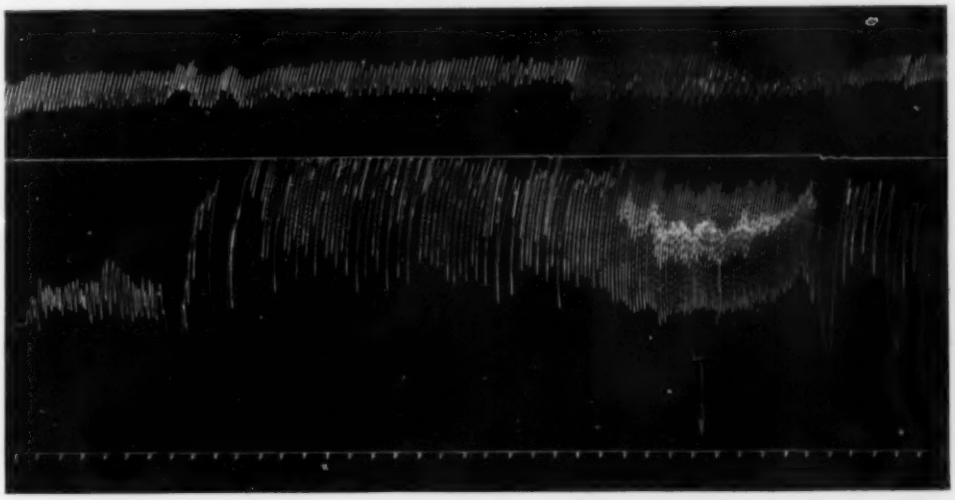

FIG. 6. Morphine analgesia. Penetration of frontal lobes with a hand drill. Reflexes present. Respirations were stimulated. Blood pressure remained about the same throughout. The animal was conscious. Spinal fluid slightly bloody with a pressure of 400 mms. Minimal effect.

expulsion of the cerebellum with such force as to lacerate that tissue. An injury with a 22 BB rifle 5 cm. below the medulla which transected the spinal cord, resulted in cerebral contusions of the cortex of the hemispheres due possibly to transmitted pressure. Finally, cerebral tissue was consistently extruded through the defect made by a bullet's entrance.

Measurement of the intracranial pressure at the time of injury by means of a fluid system attached by copper tubing to a tambour from an adapter screwed into the skull, showed only instant qualitative changes in pressure. Records of the cerebrospinal fluid pressure in the cistern at later intervals by means of a 1 mm. bore manometer showed the highest pressure to be 400 mm. of water. The average pressure was between 100 mm. and 200 mm. of water. Figure 7 is a typical record of blood pressure and the respirations, showing also the qualitative change in intracranial pressure at the moment of injury. Figure 4 shows the result after decompression of both hemispheres.

This animal survived an injury which would be fatal under the condition of a closed cranial cavity. In this instance, the increase in intracranial pressure was prevented by the decompression.

Discussion

In the above described experiments, a mechanical drill run by hand was used to penetrate the brain and three types of bullets were used for the gun-

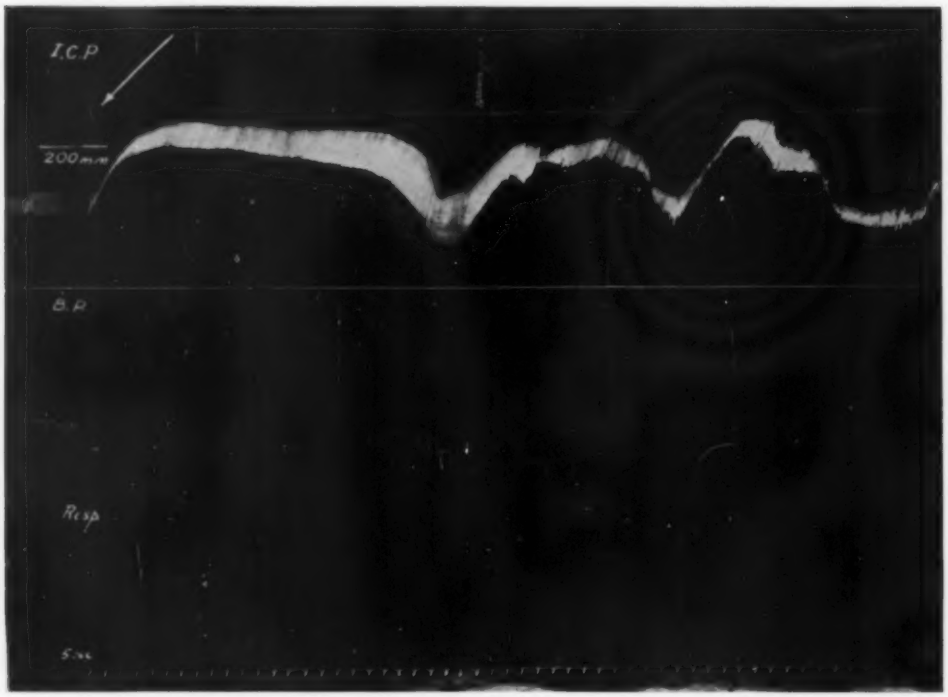

Fig. 7. Morphine analgesia. Injured with 22 revolver. The intracranial pressure recorded a sharp qualitative change at the instant of injury (see arrow). Respirations ceased and reflexes were lost temporarily. With return of respirations, there was a corresponding rise of the blood pressure suggesting that in this instance, the vasomotor mechanism was failing before the respiratory function.

shot injuries—the pellet (revolver), the 22 BB (revolver 780 ft. per sec.) and the 22 short (rifle 970 ft. per sec.). It is evident from figure one that the greater the velocity the greater was the severity of the pathological and physiological effects. Whereas with the 22 short rifle (970 ft. per sec.) only profound effects were produced, with a pellet injury, no profound effects were obtained. It should be stated that the weight of a bullet is also significant. The 22 BB shot weighs only 20 grains whereas the bullets used for the 22 short rifle were 40 grains. Therefore, the results from a gunshot injury must be ascribed not only to the velocity but also to the mass of the bullet. A relatively great velocity of an extremely small mass may produce minimal

injury while a large mass with minimal velocity may produce no significant effect. The product of mass and velocity is momentum. In our experience, the acute pathological and physiological effects of injury to the head are proportional to the time rate of change of momentum of the injuring object within an optimum range.

Sir Victor Horsley, (1) observed the effects of gunshot wounds of the brain in the experimental animal. He emphasized the significance of a bullet's rotation as it penetrated, the rotation setting up perpendicular lines of force and thus producing widespread damage. Kramer and Horsley (2) stated that death "is not, as usually supposed, due to failure of the heart, but to arrest of the respiratory movements." The changes in circulation consisted of "(a) slight initial fall of blood pressure, (b) considerable later rise of blood pressure, (c) preservation of the rhythm of the heart." The authors attributed these phenomena as due to "a gradual rise in the intracranial tension due to hemorrhage within the skull cavity"—"supervening on the primary arrest of respiration." They stated that "the action of a bullet is essentially a hydrodynamic one."

The observations which have been made are similar to those of Kramer and Horsley concerning the vulnerability of the respiratory center in gunshot wounds of the brain. The response of the blood pressure to this type of trauma was different from that reported by these observers. In our experience, a rise in blood pressure occurred which was prompt, profound and uniform in the higher velocity group of injuries. The hypertension began at the instant of injury and it was not preceded by a fall in pressure. Tachycardia and an increased pulse pressure usually accompanied the hypertension.

The lid and corneal reflexes, the respirations and vasomotor activity were deranged in direct proportion to the intensity of brain stem injury. In the profound group, the reflexes and the respirations were abolished. In the minimal group, although minor disturbances of respiratory rate occurred, reflex function appeared to be normal. Unpredictable reactions of the respirations and reflexes were noted in the moderate group. In some experiments, respiratory activity alone was lost while the lid reflexes remained active. In others reflexes only were lost. In most instances, both respiratory and reflex function were lost together and each recovered at varying and different periods. The absence of lid and corneal reflexes was always associated with coma. However, coma was also found to occur in the presence of active lid and corneal reflexes. Thus, the absence or presence of these reflexes, a criterion used by Denny-Brown and Russell (3) may not serve for evaluating the conscious state.

The acute physiological response following gunshot penetrating wounds of the brain in the experimental animal is due to an intense, momentary increase in intracranial tension at the instant of injury. The force, (known as "explosive force") (4), of a bullet transmitted to a closed, semifluid system, results in a sudden increased intracranial pressure, the intensity of which is dependent upon the time rate of change of momentum of the injur-

ing object. The increased pressure is dispersed throughout the closed system; it acts upon all tissue and it is manifested by the response of the vital medullary centers. The vital cell or center damage, recoverable or fatal, may be the direct result of this sudden pressure. Additional immediate or delayed injury to the cells may result from the indirect effects of intrinsic vascular damage and the local destructive process. When the medulla was destroyed, death occurred without hypertension because of dissolution of the vasomotor mechanism. By means of a bilateral decompression, the intracranial hypertension was partly prevented and the medulla centers were spared.

Conclusions

1. Penetrating wounds of the brain were produced in dogs under morphine analgesia by means of a mechanical drill, pellet shot, 22 BB revolver and a 22 BB rifle.

2. A sudden, intense, increased intracranial tension of brief duration at the instant of injury was observed to accompany gunshot injuries of the brain by the 22 BB revolver and BB rifle. It is felt that this increased intracranial tension is the cause of the acute physiologic effects observed.

3. The results of the injuries could be classified into profound, moderate and minimal physiologic effects. Profound effects were characterized by loss of respiratory and palpebral reflex activity, hypertension and death, the result of injury with the 22 short rifle (970 ft. per sec.). In the moderate group, the reflexes and respiratory function were temporarily interrupted; a rise in blood pressure usually occurred; some of the animals survived. This degree of injury was produced by the 22 BB revolver (780 ft. per sec.). Those in the minimal group showed no significant change in the vital functions and these animals all survived the acute experiment in which injury was produced by a penetrating drill or pellet shot.

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EXPERIMENTAL INVESTIGATION OF VISCERAL AFFERENT SYNAPSES IN COELIAC GANGLIA

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VISCERAL afferent neurons, for the most part, have their cell bodies in dorsal spinal root ganglia and their first synaptic connections in the spinal cord. The experimental evidence (8, 9, 12, 14) upon which this conclusion is based has been reviewed elsewhere (11, 15). True reflexes involving synaptic transmission take place, according to this view, only through the central nervous system. Certain experimental evidence (13), however, indicates the possible existence of reflexes mediated through 'decentralized' sympathetic ganglia, *i.e.*, those deprived of all connections with the central nervous system. It is thereby implied that within the peripheral sympathetic system are located sensory neurons, the centripetal processes of which end in sympathetic ganglia in connection with postganglionic cells, thus establishing an intrinsic sympathetic reflex arc.

The latter view has received considerable support recently from experiments on the 'decentralized' coeliac and mesenteric ganglia. Kuntz (3) observed the persistence of some synaptic connections in the coeliac ganglia of cats after "the splanchnic nerves were divided and the upper lumbar segment of the sympathetic trunks extirpated bilaterally." Bilateral vagotomy did not appreciably diminish the number of residual synapses. About two weeks were allowed to elapse between the operation and histological study. In other experiments the nerves extending from the coeliac plexus to the gut were sectioned and a few days later some degenerating fibres were found in the proximal parts of these nerves. This observation suggested the presence in the wall of the gut of afferent neurons with fibres running centripetally into the coeliac plexus. Kuntz concluded that the synaptic connections which persisted in the coeliac ganglia, following degeneration of the splanchnic nerves and extirpation of the upper lumbar chains, probably represented the termination of such centripetal fibres. Similar results were obtained in experiments on the inferior mesenteric ganglia (4). The extent of the removal of the sympathetic chains in these experiments is not indicated precisely, which makes it difficult to evaluate the completeness of the decentralization of the ganglia.

Physiological evidence in support of their histological findings was offered by Kuntz and Buskirk (5). In cats inhibition of bile flow follows distension of the distal segment of a transected loop of intestine. The reflex was unaltered by bilateral section of the splanchnic and vagal nerves, a procedure which they refer to as 'decentralization' of the coeliac plexus, despite the fact that the lumbar sympathetic chains were presumably left intact in these experiments. In the same type of preparation inhibition of

motility in the proximal segment of the transected intestine following distension of the distal segment could still be obtained in some animals after division of the nerves indicated above. The intestino-intestinal inhibitory reflex, however, could only be obtained occasionally and the evidence is by no means conclusive. Nor can one agree that "all connections of the celiac plexus with the central nervous system were interrupted."

Other experiments along the same lines have given conflicting results. Hermann and Morin (1), and Morin and Vial (10) found that in anaesthetized dogs bilateral splanchnicotomy alone was sufficient to eliminate the intestino-intestinal inhibitory reflex. Bilateral splanchnicotomy, however, does not always abolish it (17). In unanaesthetized dogs having two Thiry fistulae made from adjacent segments of the upper jejunum, Youmans, Karstens and Aumann (17) found that removal of both lumbar sympathetic chains from above the point where the major splanchnic nerves emerge, eliminated all inhibition in either intestinal segment during distension of the other segment. The same procedure abolished all pain response from intestinal distension. Bilateral vagotomy did not abolish the inhibitory reflex. Ivy and his collaborators (2, 16), on the other hand, have shown that inhibition of bile flow following distension of the colon, persisted in two dogs in which bilateral splanchnicotomy and bilateral excision of the lumbar chains had been performed, and was still present in one of these animals after bilateral vagotomy had been superimposed upon the previous surgical procedures.

One of the chief problems in interpreting the results of all such experiments is the uncertainty that the coeliac ganglia have been completely deprived of all central connections. The only sure method of decentralization is complete sympathectomy, by the method introduced by Cannon, combined with bilateral vagotomy. We have therefore reinvestigated the intestino-intestinal inhibitory reflex in such a preparation. Professor C. W. Hampel has kindly given us advice on the procedure of complete sympathectomy and participated in each operation. Preliminary studies were carried out on animals with only the splanchnic nerves cut, or the lumbar sympathetic chains removed, either on one side or bilaterally. Section of the vagi alone was also carried out in many experiments, but never had any effect on the intestino-intestinal reflex. This observation, merely confirmatory of all previous work, is not included specifically in the results.

METHODS

Recording: Cats were anaesthetized by nembutal administered intraperitoneally. A loop of jejunum, approximately 15 cm. distal to the point where the small intestine passes behind the colon, was transected together with the attached mesentery down to the large mesenteric blood vessels. A balloon (latex finger cot) was inserted into the proximal segment of small bowel and connected with a tambour for a kymographic recording of intestinal contractions. Another balloon was placed into the distal loop in order to distend the gut. The edges of the opening into the abdominal cavity were clipped together, and the animal was kept warm throughout the experiment. Blood pressure was recorded from the femoral artery. One to two hours were usually allowed to elapse before the experiment was commenced, in order to obtain adequate intestinal contractions. A fairly regular base line

of activity having been obtained, the distal segment of the jejunum was distended by inflating the balloon with 20 cc. of air for about 10–15 sec. (The volume of air was sometimes increased gradually to 45 cc. and for periods up to 40 sec.)

Decentralization of coeliac ganglia (chronic preparations): Each sympathetic chain was removed in one piece from above the stellate ganglion down to the level of the brim of the pelvis. The entire thoraco-lumbar outflow was thereby eliminated, and all splanchnic nerves, both thoracic and lumbar, divided. The excision was done in three stages. The intestino-intestinal reflexes were tested one week after the last operation. Decentralization of the ganglia was completed at the time of the experiment by dividing the vagus bilaterally, either in the neck or just below the diaphragm. The abdominal vagotomy was in some instances combined with transection of the oesophagus.

In the preliminary studies (mostly acute preparations), four principal pathways had to be considered: the right and left splanchnic nerves and both lumbar sympathetic chains. Only one of these four was cut or removed at any one time; the motility of the intestine was permitted to re-establish itself, and an attempt at inhibition, as outlined above, again tried. This procedure was followed until all four factors were removed. The order in which the nerves were cut or removed was varied in each experiment.

Splanchnicotomy: The greater and the lesser splanchnic nerves were considered together and cut as they emerged on the under surface of the diaphragm. The peritoneum on the crura of the diaphragm was opened and all the retro-peritoneal tissue stripped away from the muscle in order to be certain that all of the nerves piercing it were interrupted.

Lumbar sympathectomy: The sympathetic chain was removed from its emergence through the diaphragm down to the level of the brim of the pelvis. The first lumbar ganglia, which are above the diaphragm, placed respectively opposite the vertebral bodies of T13 and L1, are left intact by this procedure.

Results

Normal intestino-intestinal reflex: Inhibition of intestinal motility in the proximal loop was produced during distension of the distal loop of intestine in each of 15 intact cats examined. It occurred in 98 per cent of the total 61 attempts at inhibition. The inhibition was characterized by a relaxation of muscle tone, with usually though not invariably, a cessation of intestinal contractions. The latent period was never longer than 3 sec. after distension of the distal loop. The duration of inhibition was variable, intestinal activity reappearing in some instances before release of the stimulus, where the latter was maintained for longer periods (30–40 sec.).

Effect of splanchnicotomy: In all 5 animals with unilateral splanchnicotomy, 3 on the left side and 2 on the right, the inhibitory reflex persisted. Inhibition was obtained following 16 of a total of 20 distensions (80 per cent). Bilateral splanchnicotomy was performed in 3 cats, in 2 of which the inhibitory reflex could still be obtained in 12, *i.e.*, 86 per cent of 14 attempts.

Effect of lumber sympathectomy: The results were similar in all respects to those found in normal cats. After unilateral sympathectomy the reflex was produced in all of 4 cats investigated. Twenty-one of the 22 distensions were effective (95 per cent). After bilateral sympathectomy inhibition was demonstrated in each of 4 cats so prepared. The percentage of effective distensions fell, however, to 44 per cent of a total of 39 distensions.

Effect of splanchnicotomy and lumbar sympathectomy, with one of the four nerves remaining: There were 7 cats in this group. The left splanchnic nerves were intact in 3, the right splanchnics in 1, the left lumbar chain in 2, and the right lumbar chain in 1. With the exception of one of the cats in which the

left splanchnic nerves remained, intestino-intestinal reflexes could still be produced in all the other animals. As in the group in which bilateral sympathectomy had been performed, it became more difficult to obtain the reflex. Only 40 per cent of a total of 58 distensions were effective. When inhibition did occur, it differed little from that which was found in the other groups, and the latent period remained the same.

Effect of bilateral splanchnicotomy and bilateral lumbar sympathectomy: Out of 8 cats in which denervation was performed acutely and the inhibitory reflex tested immediately afterwards, inhibition could only be induced in 3 animals, and in these only 16 per cent of 51 distensions were effective. The intestino-intestinal inhibitory reflex was completely absent in 4 chronic preparations, in which bilateral splanchnicotomy and bilateral lumbar sympathectomy had been performed three months earlier.

Effect of complete decentralization of the coeliac ganglia: In 5 cats both sympathetic chains were removed from above the stellate ganglion down to the level of the brim of the pelvis, in the manner described above. All the splanchnic nerves are thereby divided. Three weeks later the inhibitory reflex was absent in every animal of this series, despite numerous trials. It may be observed in passing that the vagi were still intact at this stage of the experiments. Completion of the decentralization of the coeliac ganglia by bilateral vagotomy had one interesting result. In the intact animal distension of the intestinal loop frequently results in an immediate rise in blood pressure. This vasopressor reflex is still present after complete sympathectomy but is markedly diminished by bilateral vagotomy below the diaphragm. Nevertheless some rise in blood pressure is still perceptible after such decentralization. Presumably the afferent pathway is largely vagal, but somatic nerves in the abdominal wall may participate to a lesser degree. The latter is suggested by the fact that if the loop of intestine to be distended is lifted out of the abdominal cavity, distension no longer produces the reflex in the abdominally vagotomized animal.

Discussion

The most significant observation of the present series of experiments is the fact that no intestino-intestinal inhibitory reflex could be obtained in any of the completely sympathectomized animals or in those in which bilateral splanchnicotomy and bilateral lumbar sympathectomy had been performed three months earlier. Certainly in the former group there can be no question of any connections, other than vagal, between the coeliac ganglion and the central nervous system. The vagal pathway has been shown repeatedly not to participate in the reflex. The results give no support to the postulated existence of visceral afferent neurons with cell bodies lying in peripherally located ganglia.

Out of 8 cats, however, in which bilateral splanchnicotomy and bilateral lumbar sympathectomy was performed acutely, the inhibitory reflex could be induced occasionally in 3 animals. This difference between the results in

the acute and chronic experiment of the same nature requires further comment. The most likely explanation is the probability that the coeliac ganglia are not necessarily completely decentralized by the operation. In these preliminary studies no attempt was made to reach the sympathetic chains above the diaphragm, and the upper one or two lumbar ganglia are therefore left intact. One other possibility must be considered.

In 1874 Langley and Anderson (6), confirming an earlier observation by Sokownin, showed that if all the upper branches of the inferior mesenteric ganglia are cut stimulation of the *central* end of one hypogastric nerve results in contraction of the bladder. This does not occur if nicotine is injected intravenously or if the opposite hypogastric nerve is cut. But nicotine does not abolish the effects on the bladder of stimulating the *peripheral* end of the hypogastric, so there was presumptive evidence for a synaptic junction within the inferior mesenteric ganglion. Langley and Anderson then added two significant observations. If one hypogastric nerve is cut and time allowed for nerve degeneration then stimulation of its central end still causes contraction of the bladder with all upper branches of the inferior mesenteric ganglia divided. Thus the nerve fibres stimulated in the experiment cannot be the centripetal processes of visceral afferents whose trophic centres lie close to the bladder wall for these would have degenerated in the central end of the divided hypogastric nerve. Secondly if the section of the upper branches of the inferior mesenteric ganglia is carried out several days before the experiment, allowing time for degeneration, stimulation of the central end of the hypogastric now no longer produces any effect on the bladder. Hence the nerve fibres stimulated in the reflex must have their trophic centre above the inferior mesenteric ganglia. By section of appropriate spinal nerves proximal to the spinal ganglia, Langley and Anderson showed that the actual fibres concerned were preganglionic and probably not posterior root afferent. Further experiments by Langley (7), on similar reflexes in the sympathetic pilomotor system, led him to establish the existence of collateral branching of all preganglionic fibres, and he designated the type of reflex discussed here as 'preganglionic axon-reflexes.' Some such arrangement might equally explain the difference in results noted here between the acute and chronic experiments.

Summary

1. The intestino-intestinal inhibitory reflex can be still obtained after any of the following procedures: bilateral vagotomy, bilateral splanchnicotomy, or bilateral abdominal sympathectomy.

2. So long as one splanchnic nerve or one lumbar sympathetic chain is left intact, the reflex persists.

3. Complete sympathectomy (removal of both sympathetic chains from above the stellate ganglion down to the level of the brim of the pelvis) abolishes the reflex.

4. Immediately after bilateral splanchnicotomy and bilateral lumbar

sympathectomy the reflex can rarely be elicited. The procedure may leave some intact connections between the coeliac ganglia and the central nervous system. The possibility of preganglionic axon-reflexes has also to be considered.

5. No support is found for the postulated existence of true reflexes through the decentralized coeliac ganglia.

6. A vasopressor reflex following intestinal distension is still present after complete sympathectomy but is markedly diminished by bilateral vagotomy below the diaphragm. Presumably the afferent pathway is largely vagal, but somatic nerves in the abdominal wall may participate to a lesser degree.

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PRESSURE BLOCK IN NERVES PROVIDED WITH ARTERIAL SLEEVES*

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THE SEARCH for an improved method of re-uniting severed nerve stumps has yielded what appears to be a superior method in the use of arterial segments as splicing agents (15, 16). The cut ends of the nerve are joined without suture inside of a snugly fitting sleeve of artery, which serves the multiple purpose of holding the nerve ends together, preventing fiber escape, branching and neuroma formation, and precluding the ingrowth of fibrous connective tissue detrimental to nerve regeneration. The success of the operation and of the subsequent regeneration depends largely upon the correct fit of the artery. If the artery is chosen too wide for the given size of nerve, it fails to seal the nerve ends, and the space left between tube and nerve invites fibrosis and nerve fiber escape. In order to avoid these hazards, one would feel tempted to use arteries with a lumen narrow enough to clamp down tightly on the nerve ends. Fresh arteries are sufficiently distensible to be fitted over a nerve of considerably larger diameter, so that a firm seal between nerve and artery could be insured. However, it was soon found out that such a tight fit was harmful in that it produced permanent compression of the underlying nerve. Moreover, some arterial sleeves which at the time of operation did not seem to compress the nerve, were at a later time found to have narrowed down appreciably, causing a bottleneck-shaped constriction (see 16, fig. 7). This was never observed when aorta had been used, but was quite common with carotid or femoral arteries; *i.e.*, vessels with a muscular wall. The tightening of the sleeve resulted from a gradual contracture of its wall, which may be ascribed to a direct response of the musculature to pressor substances in the blood. This is the more plausible as vascular muscles after denervation acquire increased sensitivity toward adrenalin (2).

In view of the potential clinical value of the sleeve splicing method, the syndrome of the constricted sleeve deserved more than passing attention. The histological analysis, which revealed a number of interesting facts of more general significance, will be presented in greater detail elsewhere (17). It was the purpose of the experiments reported in the present paper to ascertain the minimum size of artery compatible with undisturbed functioning of the nerve in its interior, as well as the functional disturbances, particu-

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larly pressure block, caused by arteries below that tolerable minimum. For this purpose, long nerves, cut at a distal level, were threaded through the lumen of a small segment of artery, and then the blocking of conduction of impulses through that region was studied. Hermann (9) ascribes the earliest observations on pressure block of nerve conduction to Fontana (1797). The first work to overcome the technical inadequacies inherent in most of the earlier studies was that of Meek and Leaper (11; contains review of earlier literature), describing reversible block in frog nerves after application of uniform pressures of up to 90 pounds for less than five minutes.

Our own experiments consisted of two groups. In both a limb nerve of a rat was cut and a piece of artery was then pulled for some distance over the proximal stump. In one group, the effects of the sleeve on conduction along the nerve were studied immediately after the operation, while in the other, the examination was not made until the second week after the operation. Nerves prepared in this way were stimulated at the proximal end with "maximal" stimuli, and the resulting action potentials were recorded oscillographically from farther distal levels on either side of the arterial sleeve. Pressure block could thus be identified by the decline and eventual disappearance of the potentials beyond the sleeve. Sleeves which were not naturally constricted could be made to compress the nerve by the local application of adrenalin, and the gradual development of a pressure block could then be followed directly.

MATERIALS AND METHODS

A total of 10 white rats was used in the experiments. The sciatic nerve was exposed and either the peroneal or the tibial division was transected at the knee. The transected nerve was freed from its partner as far proximally as could be done without injury. Arteries from small donor animals had been dissected previously and kept in Ringer's solution on ice. Either the carotid or the proximal femoral artery was used. By means of a splicing clutch described previously (16), a segment approximately 5 mm. in length was slipped over the proximal nerve stump from its free end. Save for two cases examined immediately, all wounds were closed, and healed without complication. After a lapse of from 8 to 13 days, the operated nerves were again exposed, excised, and placed in a specially constructed stimulation chamber for electrical recording. All operations were done under nembutal anesthesia.

The stimulation cell consisted of a trough of lucite, cca. 1 cm. wide, 1 cm. deep and 14 cm. long. At intervals of 5 mm. silver wires crossed the trough. In the middle each wire was fashioned into a U-shaped receptacle for the nerve. Save for these bends, the wires were insulated over their full length with "Amphenol 901" cement. From the outside the wires were connected with the binding posts of a multiple selector switch box, the contacts of which were so arranged that by the turning of two dials any combinations of wires could be made to serve as stimulating electrodes and as leads. After its introduction into the chamber, the nerve rested freely on the U-shaped supports of the silver wires in air saturated with moisture.

Action potentials were amplified by means of a condenser-coupled amplifier (time constant 0.01 sec.) and were viewed and photographed on the screen of a cathode-ray oscillograph. With this apparatus it was not difficult to recognize repetitive impulses as a standing wave if their voltage was a microvolt or more. Measurements of latency from the stimulus artifact and of peak voltage were made on enlarged projections of the photographic records.

Stimuli were provided by a square-wave stimulating circuit that was triggered by the sweep circuit of the oscillograph. Pulses of less than 0.1 msec. duration were employed and were passed through a capacity-shielded transformer to reduce artifacts and render the

stimuli diphasic. The stimuli were always adjusted to a strength slightly but definitely supramaximal for the A fibers. Their adequacy was verified frequently during each experiment.

Five of the tested nerves were prepared for histological sections. They were fixed in Bouin's fluid, impregnated with silver according to Bodian, with or without Mallory's Triple Azan Stain.

EXPERIMENTAL

A. *Pressure block by adrenalin constriction of fresh arteries.* In these tests oscillographic records were taken immediately after the arterial fragment was slipped over the nerve. Two cases were studied. The nerve was transferred to the stimulation chamber from Ringer's solution and excess fluid was blotted off. The nerve was crushed just proximal to the most distal supporting wire, which also served as one of the recording leads. The positions of stimulating electrodes, arterial sleeve, and recording electrodes are indicated in the diagrams accompanying fig. 1 and 2. After constancy of the response had been ascertained, a drop of adrenalin (1:1000) was placed on the arterial sleeve, and as soon as a diminution of the action potential spike beyond the sleeve became noticeable, a series of photographs was started. The elevation of the peaks of the response over the base line was used as an index of the volume of nerve fibers conducting through the sleeve. For easier comparison, percentage values instead of absolute values were used in making the graphs, with the amplitude of the "maximal" response at the beginning of an experiment set at 100 per cent.

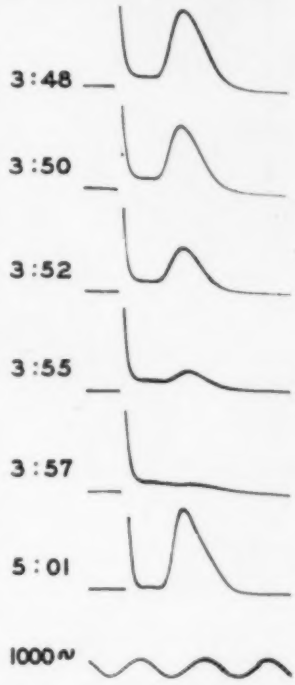

Fig. 1. Decline and recovery of oscillographic response recorded from nerve distal to constriction sleeve after adrenalin application and washing. Adrenalin was applied at 3:48. The times at which records were taken are indicated on the margin. Further details in text.

Case RA (Fig. 1 and 2) Segment of carotid artery (3 mm.) slipped over tibial nerve. Temperature 23.5°C. Records were taken alternately from a point distal to the sleeve (solid line) and a point near the proximal end of the sleeve (broken line). At both points, the action potentials dropped rapidly after adrenalin was applied (A). The reduction expresses the progressive interruption of conduction in the nerve fibers at the level of the sleeve. It is not due to a possible shunting effect of the drop of adrenalin placed upon the nerve, for neither does the application of the drop itself produce a decrease of of the amplitude, nor does the blotting off of the drop (at B) arrest further decline. Eleven minutes after adrenalin administration conduction of impulses through the area of the sleeve has practically ceased. Even at the highest amplifications, there was no evidence of impulses passing through the compressed area. The pressure block has become complete. Records from the area proximal to the sleeve have, in the meantime, dropped to about one-fourth of their original size.

In order to test the reversibility of the block, the sleeve was rinsed with Ringer's solution while remaining on the electrodes (W). At first, the response returned to only about 10 per cent. Either the sleeve had failed to relax its grip on the nerve, or the nerve fibers had been permanently damaged, or finally, the constricted nerve segment being shut off from the medium by the sleeve, had become asphyxiated. The last explanation may be discounted in view of the

shortness of the exposure. Moreover, the response recorded from a point proximal to the sleeve and fully exposed to the surrounding air likewise failed to recover. The sleeve was removed after 30 minutes (R) with the nerve left in its original position. Records taken 20 minutes later showed no significant recovery of conductivity. The nerve was then removed from the stimulation chamber and placed in Ringer's solution for the next

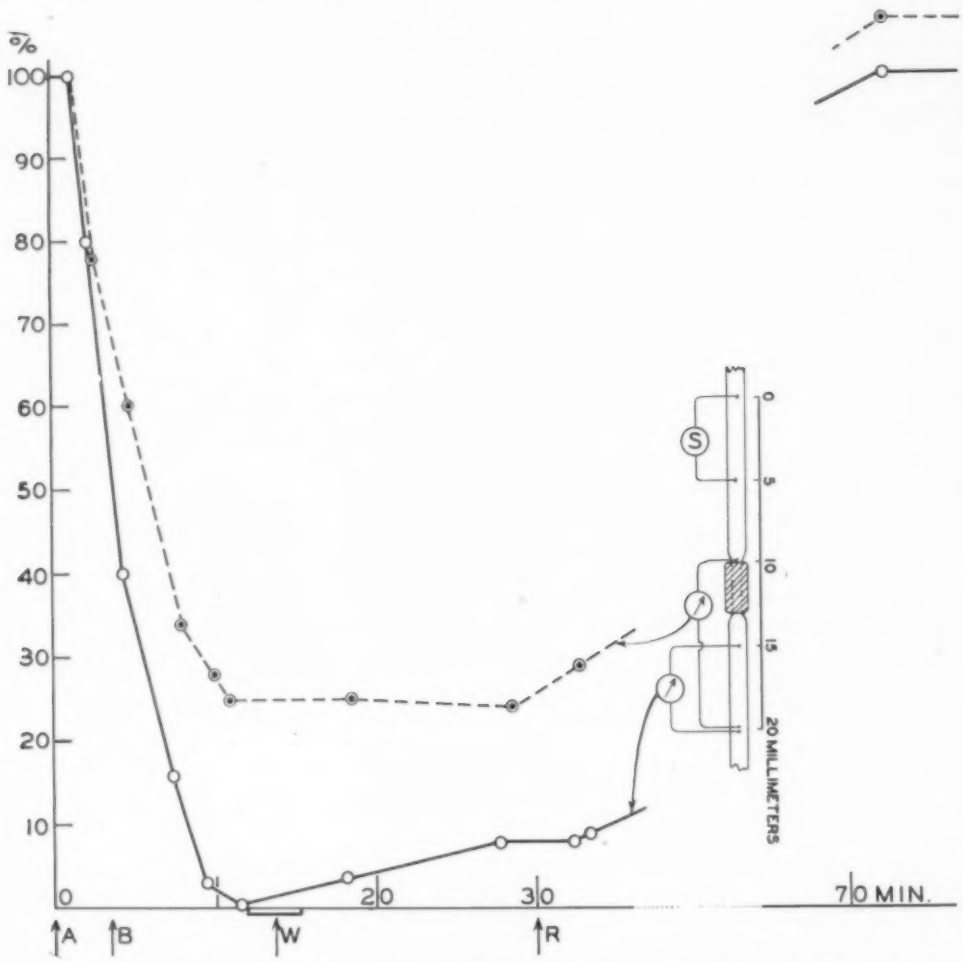

FIG. 2. Development of pressure block during adrenalin constriction of sleeve, as revealed by the decline of the amplitude of the action potentials recorded from the points indicated in the diagram, after maximal stimulation at S. Further explanation in text. Ordinates give percentage of the original size of the response at the beginning of the experiment. A, Adrenalin application. B, Blotting. W, Washing. R, Removal to Ringer bath.

twenty minutes. When returned to its original position in the stimulation chamber, it proved to have recovered full conductivity through the formerly compressed region

The sluggishness with which the pressure block disappeared is attributable to two factors: firstly, even after washing the artery relaxes only gradually, and secondly, the nerve, being relatively plastic and unelastic in its transverse direction, returns to its original diameter but slowly.

Case RB (Fig. 3) Segment of carotid artery (3 mm.) pulled over tibial nerve. Temperature

25°C. Adrenalin was put on the sleeve (A_1) and the excess fluid was sponged off three minutes later. Eleven minutes after the application of adrenalin, the response has dropped to 10 per cent of its initial size. The nerve was then washed by filling the whole stimulation chamber with Ringer's solution for three minutes (W). Records taken after the fluid had again been pumped out showed that conduction through the sleeve had not improved and that the response proximal to the sleeve, which had dropped to slightly over 40 per cent, had likewise held its level. The bath in Ringer's solution was then repeated for another three minutes but there was no perceptible change in the response. The artery was still

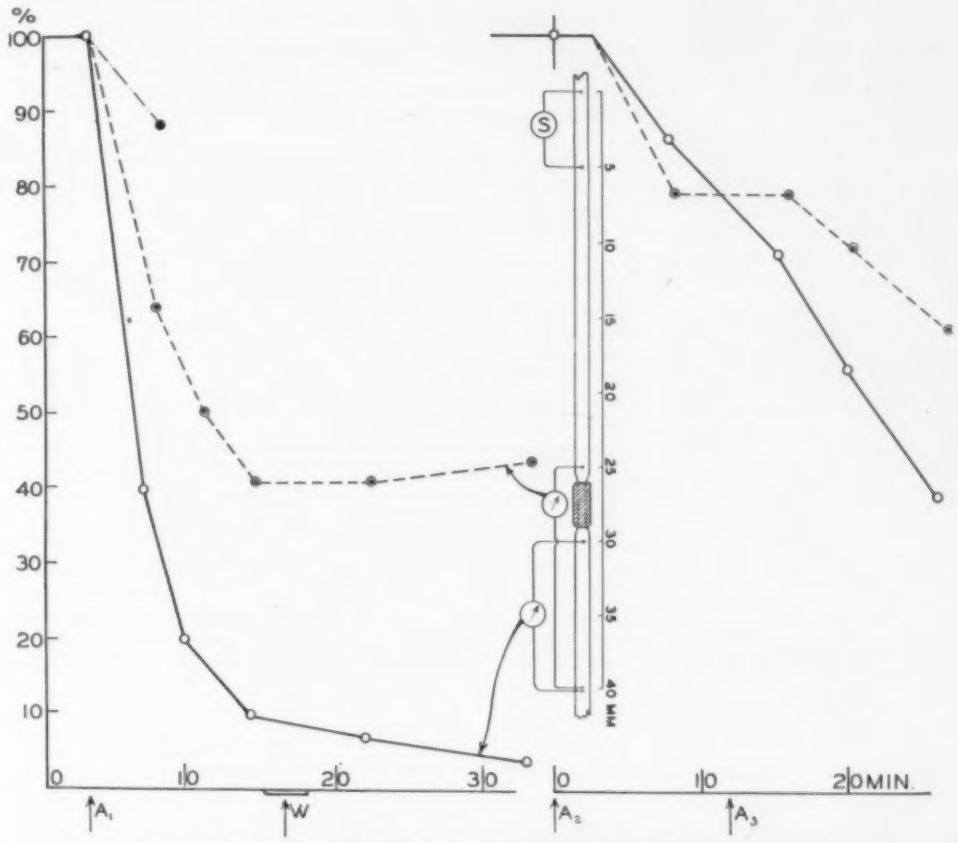

FIG. 3. Decline of the oscillographic response after adrenalin application (A) and constriction of the sleeve and recovery after prolonged washing. Symbols as in Fig. 2. Further explanation in text.

tightly clamped around the nerve with the total diameter of artery plus enclosed nerve still slightly smaller than that of the free nerve alone. Thirty-five minutes after the beginning of the experiment, the artery was stripped off. The resistance encountered in this manipulation proved that the sleeve was still actively contracted, and its mark on the nerve could be seen in the form of a conspicuous constriction. This region was then washed again thoroughly, but only an exceedingly small response had returned at 40 and 42 minutes.

The nerve was then transferred to Ringer's solution and placed in the ice box. The next morning, it was remounted in the stimulation chamber. Stimulation thresholds were found to be approximately the same as on the previous day and good responses were obtained at all points through the area of the former constriction. The temperature was 23.5°C. The arterial sleeve was then again slipped on to its position of the previous day.

Damage to some of the nerve fibers along the surface diminished the distal response as compared with the earlier determinations. In the graph, Figure 3, second half, the size of this response was set as 100 per cent. Adrenalin was then applied. As can be seen from the graph, the pressure block developed much more slowly than it did either in the same preparation on the previous day, or in case RA. Even 26 minutes after the first (A_2), and 15 minutes after the second adrenalin administration (A_3), the response distal to the sleeve had lost only 61 per cent of its amplitude. This slowness can be explained by the fact that a considerable number of fibers had been ripped off, so that the nerve was thinner than on the preceding day, rendering the arterial grip less effective.

Otherwise, case RB corroborates case RA in showing that a nerve which was exposed to a local compression block with complete interruption of conduction may gradually regain its conductivity after being released from the compressing agent. That the conduction block is due to the compression by the sleeve rather than to a direct effect of adrenalin, can be considered as certain. Not only has adrenalin never been shown to have any such blocking effect on nerves, but it has failed in our own experiments to affect conduction when placed upon the nerve directly.

The reason for the reduction of the response in the proximal nerve portion immediately adjoining the sleeve is not entirely clear. Above all, we do not know whether it indicates an actual drop in the number of conducting fibers or an increase in the shunting within the nerve, which reduces the fraction of the total action potential recordable from the surface, or possibly a distance effect of the kind observed by Gerard (6) after lcoal nerve asphyxiation. Tangl (14) and Stroebe (13) both have observed that strong compression of a nerve forces axonal substance back into the uncompressed portions of the fibers. This might cause an ascending disturbance of conductivity. However, it is doubtful whether the volume of fibers blocked proximal to the actual constriction would be large enough to account for a decline of such magnitude as was registered at this level (*e.g.*, in case RB, within 5 minutes a 12 per cent decline 6 mm. proximal to the sleeve; Fig. 3, black dot). This leaves as main explanation of the proximal decline the fact of increased shunting.

One must bear in mind that all the interstitial liquid has been squeezed from the sleeve and thereby added to the liquid content of the nerve on either side. Since, owing to the shunting effect of extraneuronal fluid, the volume of action potential recordable from the surface varies with the ratio of axonal to non-axonal nerve content, any such increase of interstitial liquid for a given fiber volume means a reduction of the recordable fraction of generated potential. The increase in fluid content of the nerve near the constriction can actually be recognized as a slight bulbous swelling, and histological studies of chronic cases show the presence of voluminous edemas (Fig. 4, 5). It, therefore, seems reasonable to ascribe most of the observed reduction of the amplitude of the records at some distance from the compression to a registration artifact rather than to real interference with conduction.

B. *Cases with chronic constriction.* Table 1 lists the 8 cases in which an arterial sleeve has been present over the nerve for from eight to thirteen days prior to the oscillographic tests. In six of them (R45, R47A, R47B, R48, R50, R51) impulses were found to be conducted no farther than the proximal end of the sleeve. No trace of conduction into and through the sleeve was ever noticed, even at highest levels of amplification. In all these cases the artery, when first placed over the nerve, fitted tightly. In the days following the operation, it had undergone further contraction, a fact which became clear from the histological preparations.

Lack of conduction through the sleeve raises the question of whether there was merely a physiological pressure block or whether the nerve had undergone degeneration. Thus, five of the six specimens were sectioned and studied histologically. The impregnation of one (R51) was unsatisfactory; the remaining four showed various degrees of degeneration, which may be briefly described.

In general, the histological appearance of these nerves duplicates some of the features described in spliced and regenerated nerves with constricted sleeves kept for much longer periods (16). These are: (i) edema of the nerve proximal to the constriction; (ii) swelling of the axons proximal to the constriction; (iii) tight packing and loss of diameter of the nerve fibers within the compression zone. As these features are discussed in greater detail elsewhere, they may be illustrated here merely by a sample case. Figure 4 shows cross sections through the nerve of specimen R50, 10 days after putting on the sleeve. The levels from which these sections were selected are indicated in the diagram, Fig. 5. All sections being photographed at an identical magnifica-

Table I

Specimen	Host weight	Nerve	Artery			Examined after days	Edema	Conduction Block		Histology	
			Name	Weight of donor gr.	Fit			Permanent	After adrenalin	Sections	Degeneration
45	210	Per.	Fem.	30	Tight	12	+	+		Long.	Complete
46	210	Per.	Fem.	220	Loose	13	–	–	+	—	—
47A	180	Per.	Fem.	65	Tight	10	++	+		Long.	Complete
47B	180	Tib.	Car.	65	Tight	10	++	+		—	—
48	180	Per.	Fem.	60	Tight	10	+	+		Long.	Partial
49	180	Per.	Car.	80	Close	8	–	–		—	—
50	180	Tib.	Car.	80	Tight	10	++	+		Cross	?
51	180	Tib.	Car.	80	Tight	10	++	+		Negative	—

tion, the variations in the diameter of the nerve become at once evident. Moreover, the graph, Fig. 5, gives the actual values of cross sectional area, as determined by planigraphy of camera lucida drawings, plotted over the length of the nerve.

Figure. 4A illustrates the almost unaffected proximal portion of the sciatic nerve; one recognizes the internal division of the nerve into a peroneal and a tibial branch, the latter being the experimental nerve to be followed in the subsequent figures. In the region of the edema, which begins about 3 mm. proximal to the sleeve, the nerve is swollen to nearly twice its proximal diameter (Fig. 4B), owing to the accumulation of large amounts of fluid in the endoneural spaces. This edema indicates, as is discussed more fully elsewhere (17), that there occurs in the endoneural spaces a persistent centrifugal seepage of fluid. The constriction of the sleeve, by obliterating the endoneural channels, causes a damming up of this fluid in front of the bottleneck, thus swelling the nerve—in the present case, to about three times its original cross sectional area. The appearance of the nerve inside of the sleeve (Fig. 4C) is in marked contrast to that of the edematous region. The fibers are tightly packed and there are few endoneural spaces left. All fibers are of small diam-

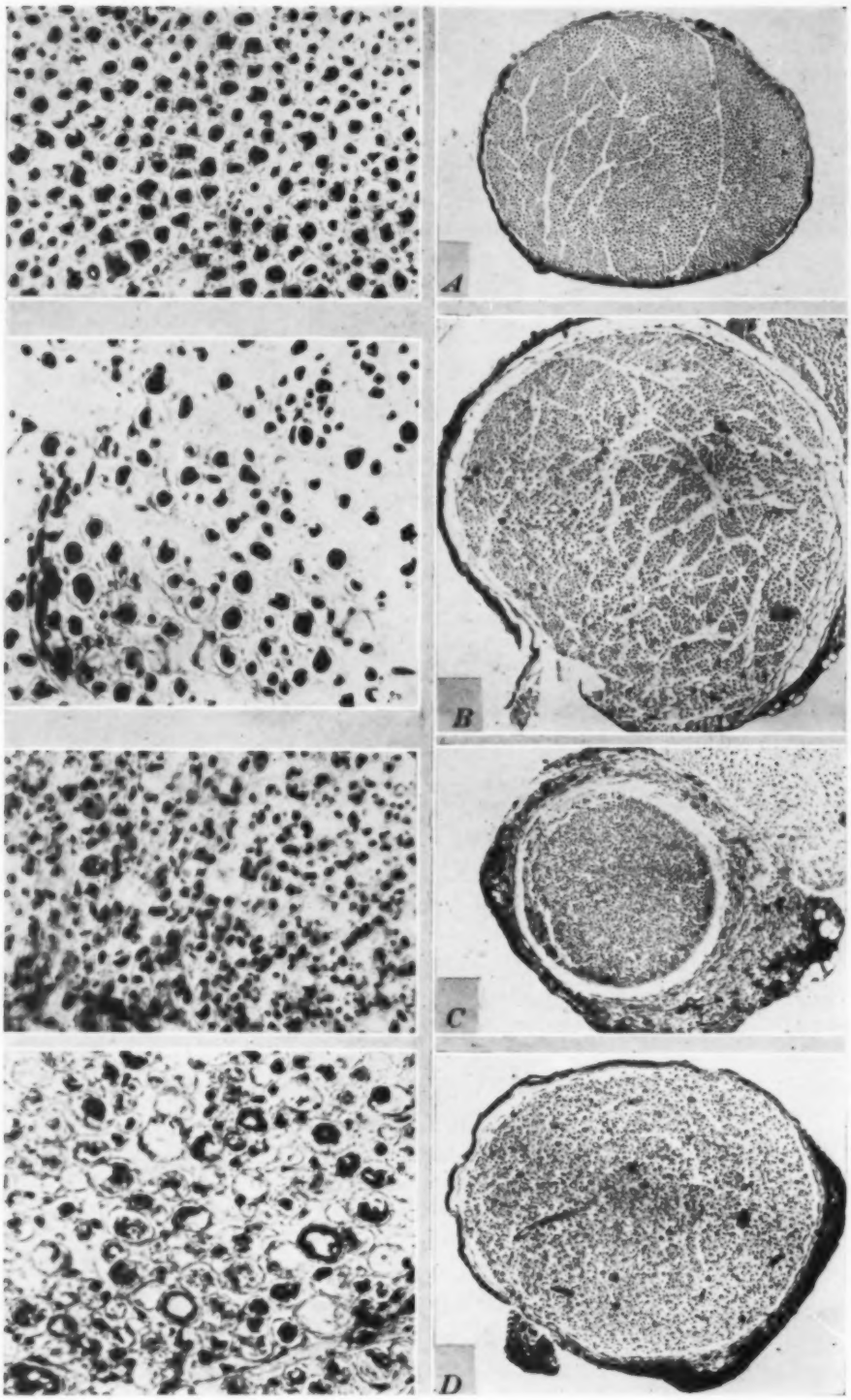

FIG 4. For legend see opposite page.

eter. Degenerating fibers, scarce at the entrance into the sleeve, appear in increasing numbers as one proceeds distally. At the exit from the sleeve, the nerve suddenly widens again and reaches a cross sectional area of about 50 per cent above normal (Fig. 4D). This peripheral swelling is definitely not due to an edematous condition, as the nerve fibers are contiguous and there is no excess interstitial fluid. Its main cause is the extensive degeneration going on in this area, the individual degenerating axons being transformed into swollen tubes of Schwann. The slight flanging of this portion, shown in Fig. 5, may be an elasticity effect. In our cases, true edematous swelling invariably appeared at the proximal, but never at the peripheral side of the constriction.

Many axons are widened at the level just proximal to the bottleneck, narrowing suddenly to the smaller caliber observed inside the sleeve. As will be shown in a subsequent paper, this phenomenon indicates that the column of axonal substance is subjected to a steady centrifugal pressure or flow.

The histology of the other 4 cases presents essentially the same picture. The only variation lies in the different proportions of intact fibers in the region beyond the sleeve. This can be better estimated in longitudinal than in cross sections. Three of the nerves, R45, R47A, and R48, have been sectioned longitudinally. All three have in common that many fibers within the compressed area are intact, with the axons continuous, of smooth contour, and well impregnated with silver; that as one proceeds peripherally, more and more fibers in various stages of typical Wallerian degeneration come into view; and that the transition

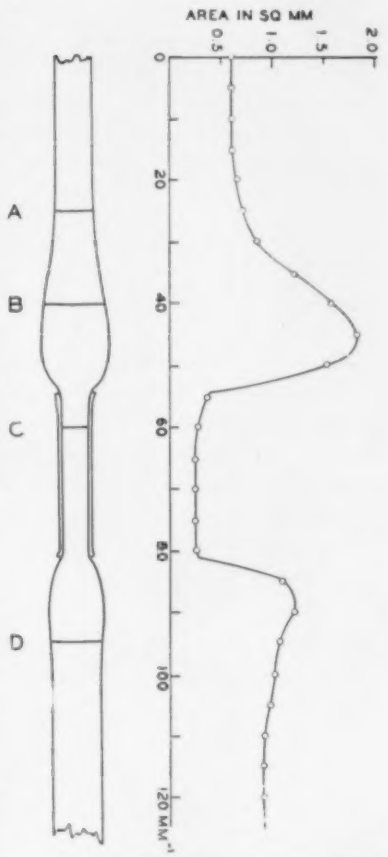

FIG. 5. Diagram of nerve, R50, constructed from measurements of the diameters at consecutive levels. In the right half of the figure, total cross sectional area is plotted over the length of the nerve from planimetric determinations made at 0.5 mm. intervals.

FIG. 4. Cross sections taken at four different levels of a tibial nerve constricted by a sleeve of artery (R50). The dimensions of the nerve and the positions from which the cross sections were chosen are indicated in correct proportions in the diagram, Fig. 5.

A, intact part of sciatic nerve; tibial division (experimental nerve) at left.

B, edematous portion of tibial nerve.

C, compressed region.

D, degenerating peripheral part.

Representative portions of each section are reproduced under higher magnification at the left.

from undegenerated to predominantly degenerated portions is fairly abrupt. At levels peripheral to the sleeve, the proportion of intact fibers is rather

FIG. 6. Photomicrographs of longitudinal sections through the compressed (top) and the farther distal portion (bottom) of the nerve, R47A. Note the number of intact fibers, mostly of small caliber, in the sleeve region (top), and the presence of numerous intact fibers of small and medium caliber, as well as of some regenerated fibers, amidst remnants of degenerating fibers in the peripheral portion (bottom).

small. Moreover, in animals R45 and R48 all fibers present are extremely fine, and there is every reason to assume that they represent regenerated rather than the original branches. This they reveal by occasional branching, certain

irregularities of their course and their position relative to the degenerated Schwann tubes. On the basis of a most conservative estimate of regeneration speed of 2 mm. per day (8) the 10 to 12 days available to these fibers after the operation would have been ample for regeneration through the 5 to 6 mm. stretch beyond the end of the sleeve, which is all there was in our preparations.

In these two cases, the apparent extinction of the impulses in the sleeve region is, therefore, readily explained by the absence of sufficiently large and numerous nerve fibers to give a recordable response. The fine newly regenerated fiber branches were imbedded in such a mass of non-axonic shunting tissue that their potentials may well have been lost before reaching the recording electrodes.

In contrast, the third case, specimen R47A, contained a much larger proportion of intact fibers in its peripheral part, and most of these could be recognized as old rather than regenerated fibers. This is indicated by their position and, above all, size, some being of medium caliber with distinct sheath (Fig. 6). Since the volume of these intact fibers passing through the sleeve into the peripheral region was large enough to have yielded a fair action potential, the fact that no trace of such activity was discernible proves that these fibers were physiologically blocked in the compressed region.

Prolonged pressure block may, therefore, exist without destroying the integrity and continuity of the nerve fiber. The fact that only one in three cases has given this result in our series, clearly indicates that the margin of pressure between one which merely blocks the nerve physiologically and one which leads to morphological degeneration is not very wide.

C. *Adrenalin constriction in transplanted sleeves.* Two cases, R46 and R49, failed to show pressure block, and conduction through the sleeve region was wholly unimpaired. The sleeves in these cases were marked at the time of the operation as fitting "loosely" or "closely" rather than "tightly." Lack of constriction was demonstrated by biopsy. Table 1 shows that these two arteries were, relatively speaking, the largest of the set. In R46, the sleeve came from a donor of the same size as the host, and in R49, it was transplanted from an 80-gram donor to the peroneal nerve of a 180-gram host. As is shown by cases R50 and R41, the same size of artery over a tibial nerve would produce pressure block, but the tibial at this level is about twice the size of the peroneal.

Conduction through the sleeve of nerve R46 being perfect, this specimen was used to test the effectiveness of adrenalin in sleeves transplanted for nearly two weeks. The experiment was done in the same manner as described for cases RA and RB. Figure 7 shows the results (temperature 23° C).

Seven minutes after adrenalin application (A_1), the response has dropped to 25 per cent of the initial size. After rinsing with Ringer's solution (W_1), the response recovered to 88 per cent. After that, records were taken not only from points distal to the sleeve but also from within the sleeve and proximal to it, as indicated in the diagram. For the purpose of easier comparison of subsequent relative changes, the second readings from the proximal points

were adjusted in the graph to the same relative strength as the simultaneous value of the distal record, *i.e.*, 88 per cent. After renewed adrenalin application (A_2), it took less than ten minutes for the distal response (at the 25 mm.mark) to decline again to about 20 per cent. Simultaneously, a less extensive decline was recorded from points 20 and 15 mm. After renewed washing (W_2), the response from beyond the sleeve failed to recover appreciably and the experiment was discontinued.

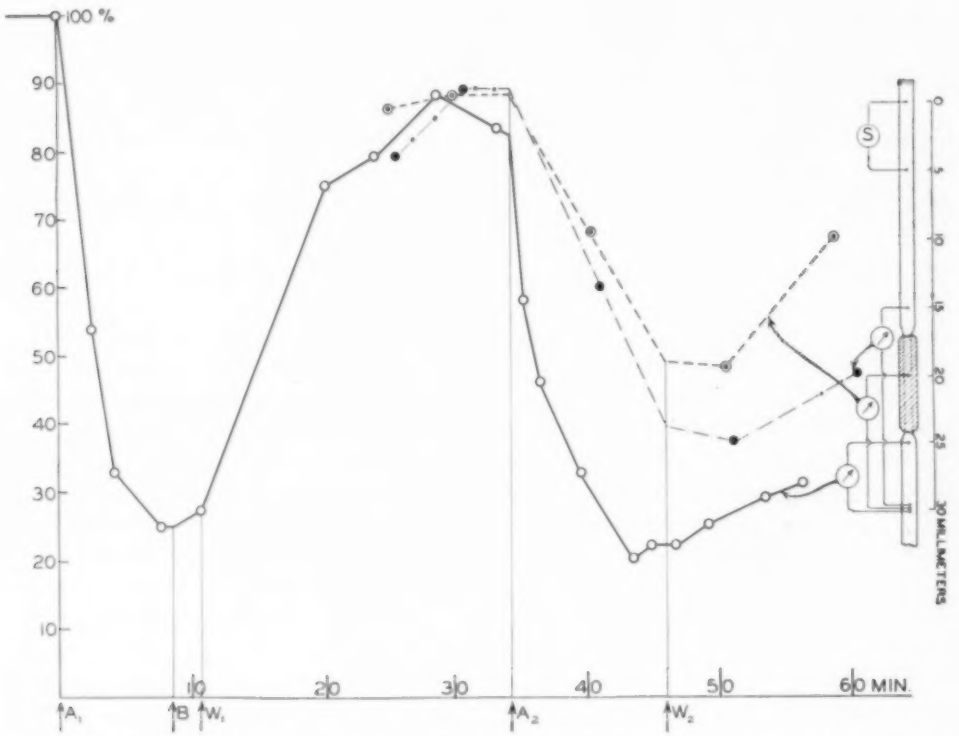

FIG. 7. Decline and recovery of action potential during adrenalin constriction and relaxation of an arterial sleeve transplanted 13 days previously. Electrode position indicated in diagram. Symbols and units as in Fig. 2 and 3. Further explanation in text.

The following conclusions can be drawn from this experiment. The transplanted segment of artery was still responsive to adrenalin after 13 days in the body. The time course according to which pressure block developed was of the same order in the fresh and in the transplanted artery. In contrast to experiments RA and RB, the first Ringer's bath produced a fairly rapid recovery of conductivity through the sleeve region. This may be ascribed either to the fact that the adrenalin was washed off before the constriction had reached its full extent, or to a slight weakening of the arterial wall after transplantation, permitting the nerve to redistend the relaxing artery and recover its former diameter sooner. At any rate, the experiment proves that a pressure

block of short duration is promptly reversible, although after a second adrenalin constriction (A_2), washing failed to have the same restorative effect as before. The response recorded from within the sleeve region (Fig. 7, broken line) declined markedly less than that recorded from beyond the sleeve (to 49 per cent as compared with 18 per cent), which reveals that at least half of the fibers, even at the height of the compression, were not blocked until in the distal portion of the sleeve. The decline of the response at the 15 mm. mark (2 mm. proximal to the sleeve) can again be ascribed to the shunting effect of nerve fluid squeezed from the compressed area.

Discussion

According to these experiments, an arterial segment pulled over a nerve may behave in three different ways, depending on its caliber. If wide enough, it may leave the nerve permanently undisturbed. If of medium width, it will not interfere with the nerve under ordinary circumstances but will clamp down and produce pressure block of varying intensity when exposed to adrenalin. If of smaller diameter than the nerve itself, it will produce permanent compression, resulting in loss of conductivity and, in more serious cases, degeneration of the nerve distal to the constriction.

In studying the development of the physiological pressue block oscillographically, we have tacitly ascribed any decline in electric response registered from the nerve beyond the constriction to the extinction of impulses in some of the fibers at the level of the block. This assumption, however, needs qualification. As illustrated in Fig. 5, compression by an arterial sleeve may reduce the nerve in its lumen to less than half its former size. Under this lateral compression, the interstitial fluid of the endoneural spaces is displaced longitudinally and squeezed into the parts of the nerve bordering on the compressed area. As this augments the non-axonal shunting material in the nerve, a certain reduction of the recordable action potential in this region should be expected. The size of any decline referable to this source can be estimated from the records taken proximal to the sleeve (dotted lines in Fig. 2 and 3). Comparing these values with the drop recorded distally, one realizes immediately that no more than a minor fraction of the latter can be ascribed to shunting.

Within 10 minutes after the initiation of the constriction of the sleeve by adrenalin, the passage of impulses through the constricted area may have become completely abolished. That the block of transmission is due to the compression, and to no other influence, is clear. Neither adrenalin applied to the nerve directly without a sleeve, nor the presence of a sleeve without adrenalin has any similar effect on the nerve. The sleeve may be left on the nerve for a considerable length of time without interfering with conductivity, yet upon applying adrenalin, the pressure block appears within several minutes.

Our graphs (Fig. 2, 3, 7) reveal a systematic trend in the development of the pressure block. They resemble logarithmic functions, which would in-

dicate that the response declines in proportionate steps within successive intervals. The initial steepness of the decline can be attributed to the fact that the large caliber fibers are the ones to succumb to pressure block first (5).

Since the pressure within the sleeves must, for physical reasons, distribute itself evenly throughout the compressed area, the localization of the actual block must be explained in terms of differences in sensitivity of the nerve fiber to the acting pressure. In case R46, for instance, many fibers conducted more than half way through the compressed zone. Other fibers are blocked farther proximally. Denny-Brown (personal communication) finds that the first morphological changes under continued pressure occur at the nodes of Ranvier. In view of the fact, however, that nerve fibers with definite signs of Wallerian degeneration may still be capable of conducting impulses (10), a precise localization of the point of pressure block from purely morphological criteria may not be possible.

A question of considerable importance is whether or not nerve compression produces an actual change in the size of the axon. In the chronic experiments of our series, the nerve was compressed to less than half its original size (see Fig. 5 and 6). If such a diminution were to be achieved merely by the obliteration of the endoneural spaces without reduction of the size of the axons, at least half of the nerve cross section would have to consist of endoneural spaces. In the rat this is definitely not the case, and part of the observed shrinkage in our cases must, therefore, be ascribed to actual decrease in the diameter of the fibers. Our histological studies seem to bear out this contention. Nerves which have been under compression for from one to two weeks show total absence of larger fibers even in the most proximal parts of the sleeve where little degeneration has occurred (see Fig. 4C and 6). If the large fibers had been destroyed, their remnants would be plainly visible. Thus the only valid conclusion seems to be that the continued compression has reduced the fiber diameters to such an extent as to bring them all into the small or medium caliber class. Similar observations have been reported by Cajal (1, p. 302) after moderate ligation of nerves.

The fact that the arterial constriction has produced physiological pressure block on the one hand, and morphological degeneration of the fibers on the other, might suggest that a common alteration of the nerve underlies both phenomena. This view is contradicted, however, by the fact that a fair proportion of nerve fibers have been able to survive a pressure block of ten days duration (case R47A). At the end of this period, the fibers were intact morphologically, yet incapable of conducting impulses across the compressed area. This, then, proves that the local change which blocks transmission in the fiber does not necessarily entail degeneration of a physiologically isolated peripheral portion. A prediction to this effect was made by Cook and Gerard (4), and the same conclusion must be reached from numerous clinical observations of nerves which have become paralyzed by the pressure of scar tissue or other constrictions. In some instances, the mere

operative removal of the scar tissue brought almost instantaneous relief of the paralytic condition and resumption of conduction in the nerve, a condition which could not possibly have been obtained if the blocked fibers had been in a state of degeneration. Likewise, some reports in the literature about crushed nerves quote time values for the recovery far too brief to have allowed for regenerative outgrowth of new fibers from the crushed area to the end organs. One would suspect, therefore, that in these cases, while the paralysis after crushing was complete, not all fibers may have been actually interrupted, the intact ones merely suffering from temporary pressure block.

The occurrence of degeneration of the peripheral parts of fibers within constricted sleeves indicates that the constriction has produced a trauma as severe as if the fiber had been transected or crushed. That Wallerian regeneration may occur even without the opening of the neurilemmal sheath has, of course been known from previous studies on ligated nerves (1, 13) and from the observations on beri-beri (3), and our present cases are merely another illustration. On the positive side, however, they give us little information about the actual cause of the degeneration. We cannot entirely exclude the possibility that ischemia may have been involved inasmuch as the strangling action of the sleeve shuts the peripheral nerve end off from circulation for as much time as is needed for collateral vascularization to become established. This, however, takes only a few days, and it is questionable whether this could cause degeneration. It is much more likely that the compression has arrested the centrifugal flow inside the axon of substances or factors vital for the maintenance of axonal integrity, much along the lines of Gerard's (7) and Parker's concept of degeneration (12). This flow can apparently still proceed in a state in which impulse conduction along the fiber is locally blocked. This we must conclude from the cases of partial degeneration with complete pressure block.

It is interesting to note that the symptoms of degeneration were much more evident in the nerve distal to the sleeve than within the sleeve itself, where the actual compression was taking place. This corroborates more extensive observations by Denny-Brown (personal communication). Cajal (1, p. 292) likewise notes that in ligated nerves the parts of the fibers directly under the ligature fail to break down. The fact is not easy to explain unless it were by the assumption that the pressure has not only paralyzed the conductive mechanism but also those properties of the nerve fiber and of the accompanying sheath cells which are responsible for the thorough transformations after trauma which we commonly call degeneration. We know that degeneration is an active process involving cell activities, and not a merely passive breakdown. It is possible that these progressive changes were inhibited either by lack of space or by interference of pressure with a more subtle mechanism.

In practical respects, these experiments underscore the importance of the correct choice of artery for nerve splicing. The choice must consider both the size of the lumen in proportion to the nerve caliber and the amount

and contractility of the musculature of the walls. It can be seen from table 1 that only arteries above a certain size qualify for a nerve of given caliber. What appears as a comfortable fit at the time of the operation may yet later develop into a tight grip owing to the contracture of the wall of the arterial sleeve, possibly sensitized to adrenalin by denervation. Moreover, a splice which might leave the nerve undisturbed for most of the time might yet, at times of great emotion or otherwise raised adrenalin level in the blood, contract and produce a partial pressure block in the nerve with undesirable consequences to the patient.

In consideration of these facts, it would seem indicated to use splicing arteries with as little musculature as possible. This can be achieved in three ways: either so-called conducting arteries may be used, such as the aorta, proximal carotid, pulmonary, subclavian; being the largest arteries, these will, of course, be useful only in very special cases, when largest nerves are concerned and arteries can be obtained from infants or fetal donors. The second possibility is to strip much of the muscular layer from the elastic intima, which can be done with a certain amount of success. The third and by far preferable possibility is to destroy the contractility of the muscular coat by methods which will not interfere with the elasticity and consistency and those other properties of the arterial wall which make it uniquely suited as a splicing agent. A method recently developed for this purpose and consisting of freezing the artery at the temperature of liquid nitrogen, drying for a week or longer in a high vacuum over P_2O_5, and then rehydrating, has given excellent results in animal experimentation* and will be reported in detail on a later occasion.

Our results impose a certain caution in the interpretation of histological pictures of regenerated nerves, in that they show that a fiber of morphologically sound appearance may yet be inoperative physiologically. Consequently, histological continuity of nerve fibers between the proximal and distal stumps of a nerve does not necessarily imply passage of impulses. Specifically, in all instances in which the regenerated fibers pass through a relatively dense fibrous or sclerotic tissue, their conductive capacity may be questioned. One must assume that under these conditions many of the fibers are strangled by the progressive condensation of the surrounding matrix and subjected to chronic pressure block. The same force will prevent them from recovering the caliber of normal nerve fibers. It is presumably by this strangling action, even more than by the less favorable conditions it creates for nerve outgrowth in general, that fibrosis forms one of the chief obstructions to functional nerve restoration. One of the main advantages of a good arterial splice lies in preventing such fibrosis from occurring.

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* The generous assistance of Professor Robert R. Bensley and Dr. Sylvia H. Bensley in freezing-drying the tissues is gratefully acknowledged.

Summary

The strangling effect of sleeves of artery pulled over peripheral nerve on the underlying nerve fibers was investigated in limb nerves of the rat. Adrenalin applied to an arterial sleeve over a nerve produces rapid constriction and, as a result, progressive pressure block of conduction. The development of this block was studied oscillographically by stimulating the nerve proximal to the sleeve with "maximal" stimuli and recording the decline of the action potential led off from distal levels during various phases of the constriction. Most or all of the fibers are blocked within 10 minutes after the application of the adrenalin. The block is reversible after washing but conductivity returns only very slowly.

Sleeves pulled over nerves of much larger caliber and left for from one to two weeks produce pressure block with total or partial degeneration of the nerve fibers distal to the level of compression. The nerve proximal to the constriction is characterized by edema, resulting from the damming up of endoneural fluid, and by swelling of the axis cylinders. Degeneration within the compressed area itself is restrained, but becomes extensive at levels distal to the sleeve. Numerous fibers may persist throughout the compressed area in histological integrity in spite of chronic pressure block. Likewise, fiber regeneration occurs throughout the compressed area.

Sleeves of wide caliber, which have not affected the enclosed nerve during the period of transplantation, produce reversible pressure block upon application of adrenalin much as do freshly transplanted sleeves.

The bearing of these findings on the method of splicing severed nerves by arterial sleeves is discussed.

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NOTE ON THE ORGANIZATION OF THE TACTILE SENSORY AREA OF THE CEREBRAL CORTEX OF THE CHIMPANZEE

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IN A RECENT PAPER on the cortical representation of cutaneous tactile sensibility in the monkey (7) an analysis of the pattern of cortical organization in terms of metameric segmentation was presented. The analysis showed (Fig. 3) that the spinal segments from T_1 through the last caudal (Ca_4) are projected to the contralateral postcentral gyrus and paracentral lobule in the same serial order as that in which they are arranged in the cord and with overlapping at the cortical level comparable in degree to that seen in the corresponding dermatomes. The serial order of the cervical segments is retained, but on projection to the cortex these segments are reversed *en bloc*. This reversal brings the cortical fields of the upper cervical segments in contiguity with the cortical fields of the upper thoracic segments, and places the cortical field of C_8 adjacent to that of the trigeminal nerve.

It was also pointed out that the reversal of the cervical projection results in two regions of metameric discontinuity in the cortical sensory sequence, that between the cortical fields of the trigeminal nerve and C_8 and that between the upper cervical and the upper thoracic fields. It was noted that the boundaries formed by these regions of metameric discontinuity apparently coincide with the division lines separating the face, arm and leg areas as defined by Dusser de Barenne's (2) strychnine method.

The study on which the analysis was based showed that the cortical sensory sequence in the monkey differs in several important respects from that currently accepted for man (3, 5). It appears probable that these differences may be accounted for by the greater difficulty of obtaining the necessary data on man rather than by a real phylogenetic variation. Evidence in support of this view may be found in the important, but little noted, paper by Sittig (6) on sensory fits in man. For a discussion of Sittig's observations see our paper on the monkey.

The purpose of the present note is to report certain observations which we were privileged to make on the chimpanzee "Dayton" after Dr. Marion Hines* (4) had explored the motor region of the precentral gyrus with electrical stimulation. Although few, the observations indicate that the sensory sequence in the chimpanzee is similar to that described for the monkey.

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* We wish to thank Dr. Hines and Dr. A. H. Schultz for the opportunity of examining this animal.

MATERIAL AND METHODS

The animal, an adult male (*Pan leucoprymnus*), 15 years old, weighing 47.17 kg., was received under ether anesthesia at the end of a day of experimentation in the Department of Anatomy (May 26, 1938). In the Department of Physiology the ether was gradually supplanted by intravenous pentobarbital-sodium. The animal survived about 4 hours under the latter anesthetic. Conditions were not as favorable for observation as in monkeys under pentobarbital-sodium and the period of survival was not long enough to permit examination of many points on the postcentral gyrus.

The methods of study were the same as those used on the monkey (7). Cortical responses were evoked by mechanical movements of hairs on various parts of the body surface or by light pressure applied to the skin. The cortical responses thus evoked were amplified electrically and visualized on a cathode ray tube.

OBSERVATIONS AND COMMENTS

The character of the cortical response evoked by moving a few hairs on the posterior aspect of the left heel near the edge of the sole may be seen in the examples given in Fig. 1. The responses were surface positive and consisted of a relatively fast component of 22 to 30 msec. duration, which began approximately 26 msec. after application of the stimulus, and a slower wave of lower amplitude which ended nearly 100 msec. after stimulation. Since the standing height of the animal, as measured by Dr. Schultz, was 129 cm., the overall conduction velocity of the fastest elements was approximately 50 meters per sec.

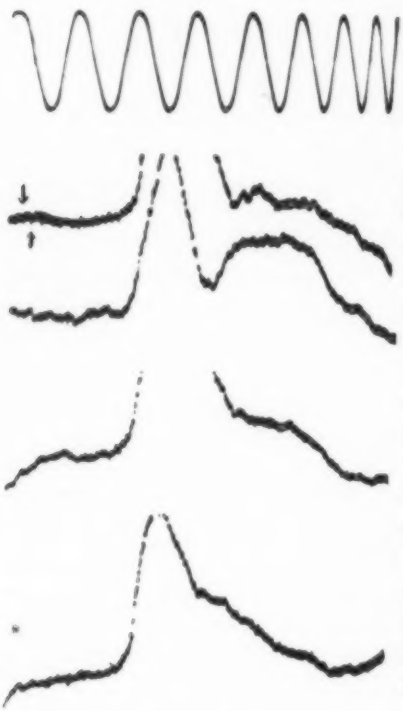

FIG. 1. Four cathode ray oscillograph traces of surface positive cortical responses evoked at HEEL point on postcentral gyrus (Fig. 2) by movement of a few hairs on posterior aspect of contralateral heel. Arrows at left indicate beginning and end of stimulus. Time signal: 60 ~ /sec.

This type of cortical response was seen at all points examined on the postcentral gyrus when the appropriate portion of the contralateral cutaneous surface was stimulated. Figure 2 shows the loci of the 7 points studied. Each of these has been labeled according to the peripheral area which, when stimulated, gave largest responses at that point. The labels on the precentral gyrus show the arrangement of the motor foci as determined for this animal by Dr. Hines (4).

Two features of the sensory arrangement are of special interest. (i) The point labeled HEEL was found to receive impulses principally from the heel and the lower posterior part of the leg—a cutaneous field which lies on the postaxial aspect of the hindlimb. (ii) Impulses from ear, occiput and anterior aspect of the neck entered the

cortex high up on the postcentral gyrus at the level of the precentral trunk area. The cutaneous area concerned is supplied by nerves from upper cervical segments. These two findings are significant and indicate that the sensory sequence in the chimpanzee is similar to that described for the monkey. The fact that the heel point in the chimpanzee is on the dorsal aspect of the

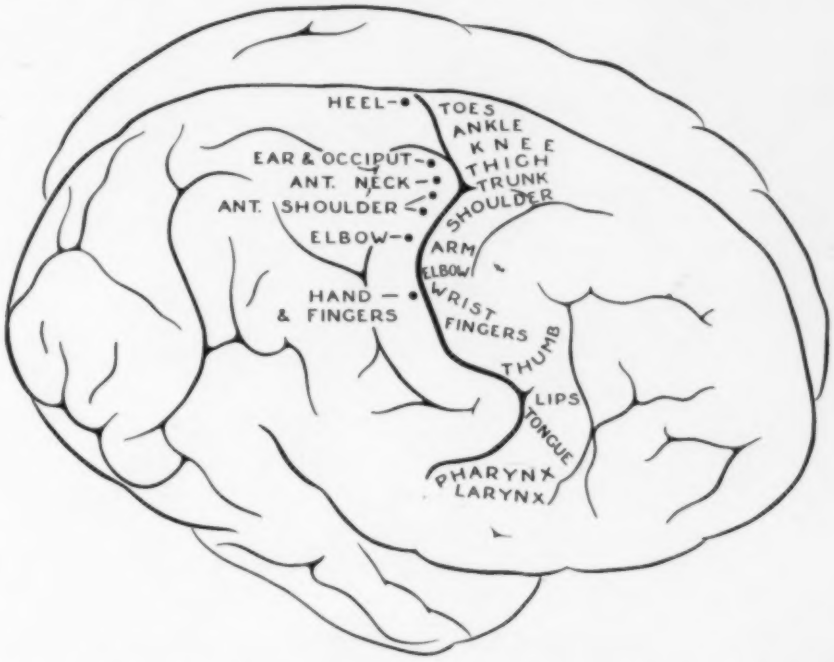

FIG. 2. Drawing (×1) of dorsolateral surface of the right cerebral cortex of chimpanzee "Dayton." Dots on postcentral gyrus mark points at which surface positive electrical responses were evoked on tactile stimulation of various portions of the contralateral cutaneous surface. Each dot is labeled to indicate the cutaneous area which, when stimulated, gave rise to largest potentials at that cortical point. Labels on the precentral gyrus show the pattern of motor localization in this animal as determined by Dr. Marion Hines (4). We wish to thank Dr. Hines for permission to reproduce her original figure with modifications.

hemisphere suggests that the sensory area for the toes is also on the dorsal surface. (Compare with Expt. X, [7].)

The relation of these observations on the chimpanzee to the pattern of representation in the monkey can be seen with the aid of Fig. 3, which represents a frontal section through the postcentral gyrus and paracentral lobule of the monkey. The sensory sequence is given by the labels placed along the surface of the cortex. Note the location of foci for occiput, ear, side of head and neck, and for the heel. The latter is on the medial aspect of the hemisphere. The analysis of the cortical arrangement in terms of metameres is shown by the overlapping heavy lines. Labels on the afferent projection fibers indicate the spinal segments to which they are related. The broken

lines at the boundaries between the fields of the trigeminal nerve and C_8 and between C_2 and T_1 correspond to the boundaries between the face, arm and leg areas of Dusser de Barenne (2). In the chimpanzee, the projection area for the upper cervical nerves (occiput, ear, side of neck, shoulder), as indi-

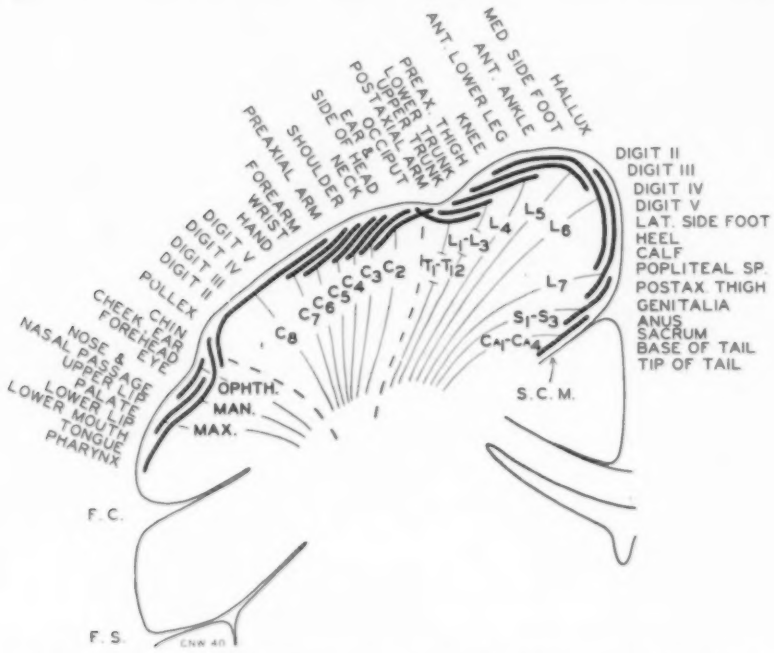

FIG. 3. Diagram to scale of frontal section through the postcentral gyrus and paracentral lobule of the monkey, giving the sensory sequence and showing, according to our analysis, the serial arrangement on the cortex of the dermatomic projection and the overlap of cortical areas for successive dermatomes. Note the reversal of the cervical projection as compared with the projection of segments T_1 through Ca_4. The broken lines at boundaries between the cortical areas for the trigeminal nerve and C_8 and between C_2 and T_1 correspond with the boundaries between the face, arm and leg areas of Dusser de Barenne (2). F. S., Sylvian fissure; F. C., central fissure; S. C. M., calloso-marginal sulcus; MAX., maxillary division of n. trigeminus; MAN., mandibular division; OPHTH., ophthalmic division; C., cervical; T., thoracic; L., lumbar; S., sacral; Ca., caudal. (From (7.))

cated by our observations, lies adjacent to the boundary between the arm and the leg areas as defined for this species by Dusser de Barenne, Bailey, Garol and McCulloch (1). It is apparent, therefore, that this boundary line in the chimpanzee, as in the monkey, coincides with the region of metameric discontinuity (between C_2 and T_1) produced by *en bloc* reversal of the cervical spinal segments on projection to the cortex.

SUMMARY

Although few, the observations here reported indicate that the tactile sensory area is organized in the same way in the chimpanzee as it is in the monkey. In the latter, analysis of the cortical pattern in terms of metameres

showed that all spinal cord segments below C_8 are projected to the cerebral cortex in their spinal sequence, whereas the cervical segments on projection are reversed *en bloc*. This produces two regions of segmental discontinuity in the cortical sequence. These regions coincide with the boundary lines separating Dusser de Barenne's face, arm and leg areas.

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NEURON PATTERNS CONTROLLING TRANSMISSION OF IPSILATERAL HIND LIMB REFLEXES IN CAT

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THE SEGMENTAL REFLEX discharge (7, 31, 21) must be considered of anatomical rather than functional significance in that it contains, in unnatural combination, those elements which constitute the several distinct ipsilateral reflexes. In the present paper are the results of experiments designed to resolve the segmental reflex into its functional components. The observation that a major division of the segmental reflex into its direct (two-neuron-arc) and indirect (multineuron-arc) components followed segregation of muscle afferent and cutaneous afferent fibers for afferent stimulation (21) provides the point of departure for the experiments to be described. Some of the present observations have been mentioned briefly in a preliminary note (23).

A general discussion of these and other results will be found in another paper (25).

The afferent fibers of the A group (14) exhibit a range of diameters extending from 20μ to 1.5μ (36). In a dorsal root the whole range of fibers is present, but in the peripheral nerves significant segregations are found (36, 8, 29, 14) which permit a degree of selective stimulation of the various components (21). For the purposes of the present discussion the afferent fibers will be classified into groups, each group being marked by a peak in the fiber distribution plots of one or another of the several peripheral nerves. Group I consists of the largest afferent fibers, which are to be found only among the afferent fibers arising from muscle. Approximately these fibers range from 20μ to 12μ in diameter (8, 29), with a distribution peak at 15 to 16μ. Group II contains fibers of approximately 12μ to 6μ in diameter, with a mode at 8 to 9μ. These fibers form a prominent peak in the fiber distribution plots of cutaneous nerves (8, 30, 14), but they are poorly represented among the muscles afferent fibers (8, 29). Group III consists of fibers gathered about a peak at 3 to 4μ (the delta pile). These last are to be found in both muscle and cutaneous nerves. Another category, to consist of the C fibers, the afferent and reflex function of which is proven (3, 2), should be included as group IV. These fibers have not been studied during the course of the present experiments.

Since group I and group II fibers are the lowest threshold fibers in muscle and cutaneous nerves respectively, they may be excited in isolation by the simple expedient of selecting the appropriate nerves for stimulation (21). There is no means at present of stimulating group III fibers in isolation but their contribution to reflex action, on stimulation, is easily recognizable as addition to the reflex discharges caused by stimulation of the larger, lower threshold fibers [after-discharge?.] (45)

The experiments were performed on cats, made spinal by transection accomplished through the dorsal atlanto-occipital membrane under ether anaesthesia, after which artificial respiration was instituted and the anaesthetic discontinued.

Group I reflexes. The reflex discharge resulting from stimulation of group I afferent fibers has been studied chiefly, but not exclusively, in connection with the nerve supply to the gastrocnemius muscle. Several considerations prompted this choice, not the least among which is the fact that the afferent fibers from this muscle have been examined by histological means (8, 29). Moreover, the gastrocnemius muscle is supplied through the seventh lumbar (L7) and first sacral (S1) segments of the spinal cord, which provides a favorable site for study by virtue of the length of the nerve roots pertaining to those segments.

Figure 1A illustrates the reflex discharge, recorded from the S1 ventral root following stimulation of the nerves of the gastrocnemius muscle. The

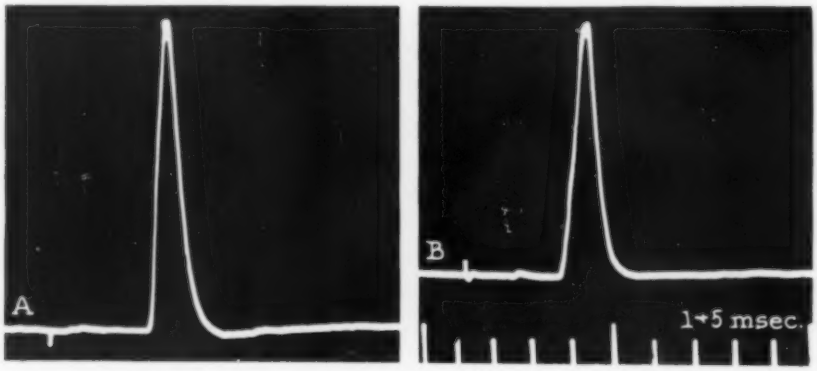

FIG. 1. Group I reflex. A—reflex discharge recorded from the S1 ventral root on stimulation of the gastrocnemius nerves. B—reflex discharge recorded from the gastrocnemius nerves on stimulating the S1 dorsal root. Time in 1 and 5 msec. intervals. In all figures where there are two time designations these are for the small and large divisions respectively.

ventral roots supplying the muscle were severed distally in order to record the reflex and to prevent the penetration of the inevitable antidromic volley into the spinal cord. Under these circumstances the gastrocnemius nerves are connected with the spinal cord only through the dorsal roots, and may be regarded therefore as 'afferent' nerves. Figure 1B presents the reflex discharge obtained by stimulating the S1 dorsal root while recording from the gastrocnemius nerves. The dorsal root was severed distally to prevent the dorsal root volley from coursing antidromically into the gastrocnemius nerves. Under these circumstances the gastrocnemius nerves may be regarded as 'purely efferent' in function. The reflex discharge from the dorsal root to the gastrocnemius motor fibers is essentially similar in latency and duration to that from the gastrocnemius afferent fibers to the ventral root. The conduction length of the reflex pathways is similar for the experiments illus-

trated in Fig. 1A and B, and so therefore are the central delays. The reflex discharges in Fig. 1 have a latency of approximately 2.6 msec., which is appropriate for reflexes transmitted through arcs of two neurons, considering the overall length of the pathways involved. Figure 2 presents an estimate in greater detail of the central delay of a reflex discharge comparable to that illustrated in Fig. 1A.

The gastrocnemius nerve to S1 ventral root reflex latency for the experiment illustrated in Fig. 2 is 2.5 msec. In the inset (B) of Fig. 2 the conduction time for the long afferent limb of the reflex is recorded by the use of leads, one placed on the dorsum of the spinal cord at the root entry zone of the (intact) S1 dorsal root, the other on nearby cut bone. By measurement, afferent conduction to the spinal cord requires 1.4 msec. By subtraction, 1.1 msec. is required for conduction in the intraspinal course of the dorsal root fibers, for synaptic delay, and for ventral root conduction. Of these events ventral root conduction accounts for approximately 0.3 msec. The remainder, 0.8 msec., may be designated as central delay, *i.e.* synaptic delay and central conduction. A central delay of this order of magnitude forces the opinion that arcs of two neurons are involved (27, 31). The total duration of the reflex spike-potential is 1.45 msec.; the total conduction distance approximately 19 cm.; the band of fibers active extends approximately from 20μ to 12μ. If the duration of the single axon spike is taken as 0.5 msec. (14), the total reflex has a dispersion of approximately 0.95 msec. Now, at 19 cm. conduction, a volley, initially synchronous, would have, on travelling in a group of fibers varying from 20μ to 12μ in diameter, a dispersion of 1.05 msec. calculated by using the conversion constant of 6 proposed by Hursh (17) to derive conduction velocity from diameter. Granting that some or all of these figures may be approximations, the dispersion encountered in experiment with the *reflex* discharge is within the limit calculated for simple transmission along an equivalent nerve bundle. There is, in consequence, reason to suppose that the reflex two-neuron-arc pathways alone can account for the group I reflex discharges that have been described.

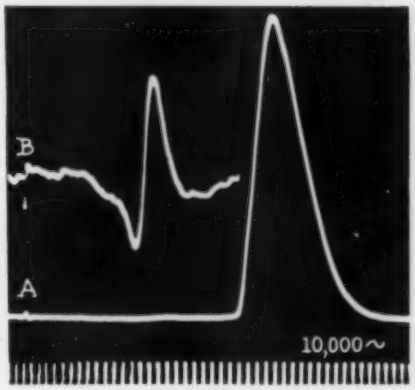

FIG. 2. Group I reflex. A—reflex discharge recorded on S1 ventral root on stimulation of the gastrocnemius nerves. B—afferent volley evoked by stimulation of the gastrocnemius nerves and recorded from the dorsum of the spinal cord at the root entry line. The difference in latency of A and B measures the sum of central latency and ventral root conduction time for the reflex discharge. Time 10,000 cycles.

The two-neuron-arc discharge reflects into the stimulated muscle nerve. When stimulating and recording leads are placed on the same nerve, with all central connections to the spinal cord intact, a two-neuron-arc discharge may be recorded, as illustrated in Fig. 3A. The stimulated volley courses

centrally in both afferent and motor fibers, and since these fibers are in general similar in the case of the group I reflexes, the reflex afferent volley and the antidromic volley will reach the spinal cord essentially in simultaneous combination. Only a small fraction of the reflex volley under these circumstances (22), however, intermediate strengths of stimulation can be found which provide a sufficiently large afferent volley to produce a reflex without blocking too many of the reflex pathways by virtue of the antidromic volley The use of a large nerve trunk facilitates the adjustment of the stimulus to attain this end.

At this point a note relative to the dorsal root reflex is in order. In many of

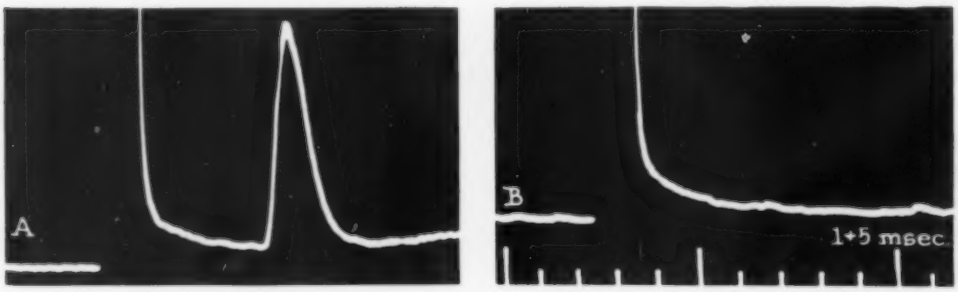

FIG. 3. Group I reflex. A—reflex volley stimulated and recorded on the tibial nerve. B—the same stimulation after transecting the L7 and S1 dorsal roots of the same side to confirm the reflex nature of the discharge. The 'tail' of the directly conducted volley is seen in both A and B. The time relations of the reflex volley show that it is transmitted through arcs of two neurons. *Cf.* also Fig. 9, 10 for other examples of two-neuron-arc reflex transmission into the stimulated nerve.

the present experiments afferent fiber pathways between the stimulating and recording leads exist to provide potential paths for the transmission of dorsal root reflexes to the recording leads. This is the case particularly when recording from the stimulated peripheral mixed nerve (44). As the central latency of the dorsal root reflex is 4 msec. (44), it does not interfere with the recording of group I reflexes, but it may appear in the nerve later to mimic other true reflex discharges. In practice, the temperature of the preparation is maintained as near normal as possible to minimize the dorsal root reflex.

In Fig. 3A is shown the reflex discharge through two-neuron-arc pathways as recorded on the tibial nerve on stimulation of that nerve. The reflex discharge follows by approximately 4.0 msec. the volley conducted directly from stimulating to recording electrodes. The added latency for this reflex over that found when the reflex is recorded on a ventral root (Fig. 1, 2) is approximately 1.5 msec., which is just sufficient to account for the added efferent conduction distance from the ventral root to the recording leads on the tibial nerve (*cf.* also Fig. 9A, G for a similar reflex discharge recorded from another preparation). Figure 3B shows that the two-neuron-arc discharge is removed by section of the appropriate dorsal roots. After section

of the dorsal roots there may be a slight residual discharge, which is due in part to a recurrent or 'pseudo-reflex' volley from the central regions of the motoneurons as a result of the uncurtailed antidromic volley (32, 22), and in part probably to discharges arising in the manner of the Hering phenomenon at the cut ends of the dorsal roots (15, 34, 20), possibly by the action of negative after-potential. Whatever the residual discharges may represent, Fig. 3B provides the essential control to show that the centrifugal volley in Fig. 3A is a true reflex volley rather than a recurrent volley of similar time relationships (32, 22).

The two-neuron-arc reflex discharge does not reflect into muscle nerves other than the one stimulated. In Table 1 is to be found a list of reflex pathways from one nerve to another which have been searched for two-neuron-arc

Table 1. Reflex pathways without two-neuron-arc reflex discharges

Stimulated nerve	Recorded nerve	Remarks
Gastroc. lat.	Gastroc. med.	Fig. 4B and C
Gastroc. med.	Gastroc. lat.	Fig. 4E and F
Gastroc. (med. and lat.)	Tibial (less gastroc.)	Fig. 4H and I Fig. 8B and C
Tibial (less gastroc.)	Gastroc (med. and lat.)	Fig. 4K and L
Peroneal	Gastroc.	No reflex or very small delayed discharge, possibly a dorsal root reflex
Gastroc.	Peroneal	Fig. 7F, G, H, I. Group III reflex, sometimes group II reflex.
Sciatic (less gastroc.)	Gastroc.	No reflex discharge
Hamstring	Gastroc.	No reflex discharge
Tibial	Peroneal	Fig. 4M, 9. Group II and group III reflexes.
Peroneal	Tibial	Very small late discharge, possibly dorsal root reflex or residual ipsilateral extensor discharge.
Superficial peroneal	Deep peroneal	Late discharges.
Tibial	Tibialis anterior	Fig. 10. Late discharges.
Tibial	Deep peroneal	Fig. 11. Late discharges.
Peroneal (less tibialis anterior)	Tibialis anterior	Late discharges. Group II reflexes.

reflex discharges to no avail, together with references to the several figures containing illustrative records.

Figure 4 illustrates the absence of reflex discharges from one to another of the divisions of the tibial nerve, even at strengths of stimulation calculated to recruit all the A fibers of the stimulated nerve into the 'afferent' volley. Record M of Fig. 4, for which the tibial nerve was stimulated while recording from the peroneal nerve, serves as a control for the viability and patency of the central portions of the reflex system in the experiment illustrated. It will be noted that the discharge recorded in 4M has a latency of 5.8 msec., whereas the two-neuron-arc discharge should appear, as in Fig. 3, with a latency approximating 4.0 msec.

Particularly interesting among the observations of Fig. 4 is the fact that no reflex is obtained as between the nerves to the two heads of the gastrocnemius muscle. At this juncture one should recall the experiment originally performed by Sherrington (41, 42), and confirmed by Liddell and Sherrington (18) and again by O'Leary, Heinbecker and Bishop (29). In each case the effect of stimulating the central end of the severed nerve to one head or

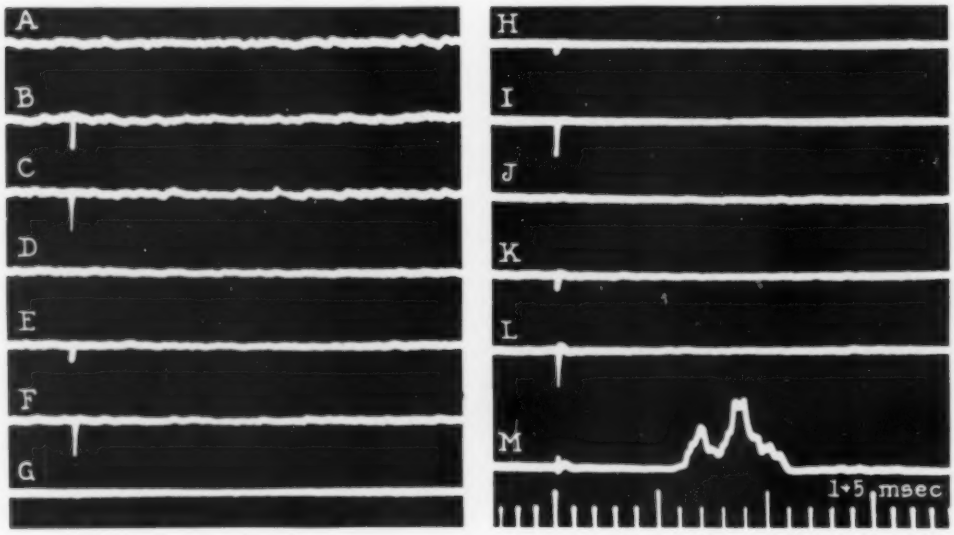

FIG. 4. The two-neuron-arc discharge is not transmitted to muscle nerves other than the one stimulated (cf. also Table I and Fig. 7, 8, 9, 10). Group II and group III reflexes are not recorded ordinarily from extensor nerves (*cf.* also Fig. 8). A, D, G, J—blank sweeps with recording leads on the gastroc. med., gastroc. lat., tibial, and gastroc. nerves respectively. B, C—weak and strong stimulation of gastroc. lat. N. recording gastroc. med. N. E. F. —Similar to B, C but stimulating and recording leads interchanged. H, I—stimulation of N. gastroc. recording on N. tibial (less its gastroc. branches). K, L—similar to H, I, but stimulating and recording leads interchanged. M—stimulation of tibial N. recording from peroneal N.—group II reflex.

fraction of a muscle (gastrocnemius or quadriceps) was inhibition of the innervated remainder of that muscle, gauged on a background of decerebrate rigidity or crossed extensor reflex. At the time these experiments were performed it was not realized that the antidromic volleys unavoidably transmitted centrally to the central portions of the motoneurons could effect the transmission of reflex effect through neighboring motoneurons not involved in the antidromic volley (32). The effect, usually inhibitory, is particularly potent as between motoneurons supplying parts of the same muscle. There can be little doubt that this action of antidromic volleys accounts, in good measure, for the observations of Sherrington, Liddell and Sherrington, and O'Leary, Heinbecker, and Bishop. Of course, the possibility of direct inhibition in the orthodromic sense (19, 21) cannot be neglected but the crucial experiment has not yet been devised to demonstrate direct orthodromic inhibition in this situation.

In spite of the known antagonism between the reflex arcs to the several heads of a muscle, and the fact that this antagonism is exerted when the interacting volleys arrive at the motoneurons in concert, the action cannot contribute significantly to the absence of two-neuron-arc discharges from one head to another within a muscle (Fig. 4B, C, E, F) or from one nerve to another (Fig. 4H, I, K, L, 7, 8, 9, 10, 11) for the depressent action of antidromic volleys is not great for the two-neuron-arc reflex at the time relationships which obtain in the present experiments, *i.e.* (virtually simultaneous combination of the afferent and antidromic volleys at the spinal cord).

From the experiments described it is possible to conclude that the afferent limb for the mediation of two-neuron-arc reflex discharge consists of the large, low threshold group I afferent fibers arising in muscle (*cf.* also 21), and that the two-neuron-arc discharge reflects only into the muscle group of muscles or head of a muscle, the afferent fibers of which are stimulated. Of course it is reasonable that, on the occasion of further subdivision of a muscle nerve twig, a stage might be reached, perhaps fortuitously, in which two-neuron-arc discharges could be obtained by stimulation of one subdivision while recording from another. The endeavor to achieve this state of subdivision has not been pursued.

One cannot escape the identity of distribution that obtains between the two-neuron-arc reflex discharge and the myotatic reflex (18). In effect the two-neuron-arc connections appear to constitute the pathway for mediation of the myotatic reflex. The relatively synchronous discharge evoked in this pathway by single shock stimulation would then imitate the phasic response to stretch (*i.e.*, the tendon-jerk) in its most brief, and possibly unattainable (*cf.* 12, 24) form. Further direct evidence for this position is to be found in another paper (24).

A comparison of group I and group II reflex effect. While the local reflex effect attending stimulation of group I fibers is confined to two-neuron-arc pathways, the reflex discharge following stimulation of a cutaneous nerve or of the medium threshold fibers (cutaneous for the most part) of a mixed nerve, has all the attributes of the multineuron-arc discharge as encountered in the segmental reflex (21). Furthermore, the distribution of the reflex evoked by stimulation of the cutaneous afferent fibers is quite different from that of the group I reflex.

In Fig. 5 are compared the effects of stimulating group I and group II fibers, as recorded from the dorsum of the spinal cord after the manner of Gasser and Graham (13) and of Hughes and Gasser (16). Figure 5A characterizes the events on stimulation of the nerve to the medial head of the gastrocnemius muscle, the appropriate ventral roots being severed. Recorded with the same electrode positions, Fig. 5B illustrates the events on stimulation of the sural (external saphenous) nerve. Fig. 5C shows the recorded result of combined stimulation of the two nerves. The conduction distance from the stimulating electrodes to the spinal cord was so arranged as to be equal in the two nerves. Study of Fig. 5 reveals that the group I

afferent volley is recorded from the dorsum of the spinal cord as a triphasic variation (*cf.* 13) practically devoid of an associated and ensuant negative intermediary potential, whereas, in contrast, the smaller group II spike potential is followed immediately by a prominent negative intermediary potential, signalling internuncial activity. In 5C, on the occasion of simultaneous stimulation of the two nerves, all the elements occurring severally in records A and B are present in approximate summation, which indicates a rather high degree of independence between the two reflexes under the conditions of the experiment (*i.e.*, with synchronous stimulation) and among the elements that contribute to the cord potential as recorded from the cord dorsum (but *cf.* Fig. 12 for interaction at another interval of shocks. Comparison of Fig. 5, 6 and 12 illustrates the fact that the reflex effect of the cutaneous nerve stimulation, the flexor reflex, is prepotent).

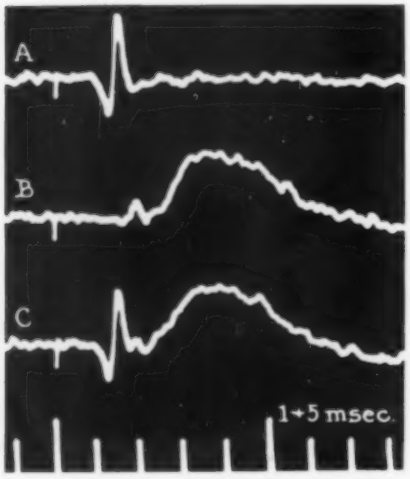

FIG. 5. Records from the dorsum of the spinal cord. A—the nerve to the medial head of the gastrocnemius muscle is stimulated. B—stimulation of the sural nerve. C—combined stimulation of the gastroc. med. N. and the sural N. Note longer conduction time for sural nerve volley than for gastroc. med. nerve volley, and negative intermediary potential evoked by sural nerve stimulation.

Figure 5 emphasizes the different conduction characteristics of the group I and group II afferent volleys. The difference in latency of conduction amounts to approximately 0.4 msec. with conduction distance of 12 cm. It is important, therefore, to make corrections for differential afferent conduction velocities when comparing the time relationships of group I and II reflexes, the correction value of course increasing as the afferent limb of the reflexes is increased in length.

The reflex discharges evoked by stimulation of group I and group II afferent fibers, and as recorded from a ventral root are quite different (21). Figure 6 shows such reflex discharges, both severally and in combination. Record A of Fig. 6 shows the group I reflex on stimulating the gastrocnemius nerves. Records B, D, F, H, illustrate the group II reflex similarly recorded in isolation, and resulting from stimulation of the sural nerve. There is random variation in the response from one observation to another. In records C, E, G, I the two reflexes are combined by synchronous stimulation of the gastrocnemius and sural nerves. The conduction distances are equal. Again, there is variation from one observation to another, but there is apparently no systematic change to suggest that the transmission of the gastrocnemius (*i.e.*, extensor) two-neuron-arc discharge has had any definite effect, one way or the other, on the succeeding discharges. The reflex evoked by sural nerve stimulation is directed into flexor channels (43). It is an important consider-

ation that the extensor two-neuron-arc reflex and the flexor multineuron-arc reflex evoked by a single *synchronous* stimulation are virtually independent, for this combination will occur on stimulation of a mixed nerve such as the tibial nerve even though only the flexor discharges are recorded, as when the recording leads are directed to the peroneal nerve (*cf.* Fig. 9). With combined stimulation, the two-neuron arc discharge is unhindered for, travelling in afferent fibers of the highest velocity, it finds the spinal cord in the 'resting' state.

Observations made from the dorsum of the spinal cord (Fig. 5) and from a ventral root (Fig. 6) under similar circumstances invite comparison. It

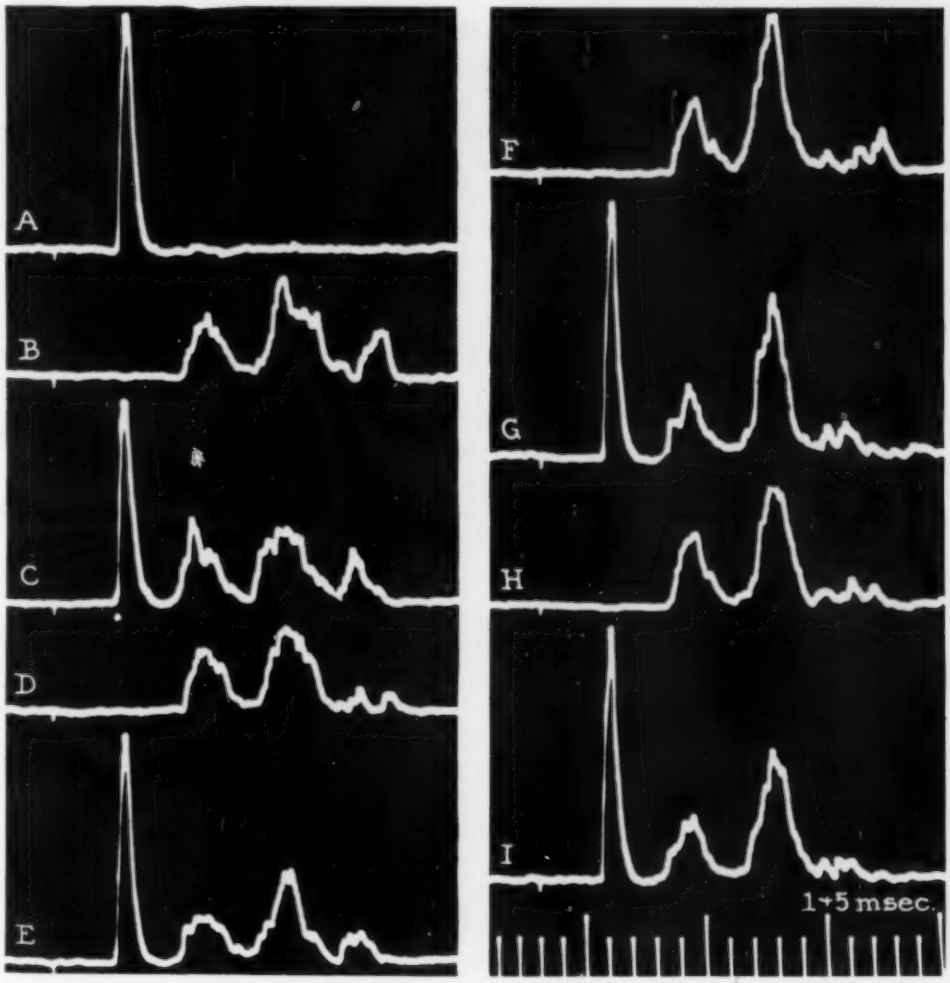

FIG. 6. Records from the S1 ventral root. A—stimulation of gastroc. nerves—group I reflex. B, D, F, H—stimulation of sural nerve—group II reflex. C, E, G, I—combined stimulation of gastroc. and sural nerves. The discharge of the group I reflex appears to have no systematic effect of the group II reflex which follows.

will be seen on comparing Fig. 5 and 6 that the group I reflex transmitted in its entirety is not accompanied by activation of the internuncial elements contributing to the cord potential (13, 16). On the contrary, the group II afferent fibers when stimulated yield intense activity among the interneurons of the dorsal regions of the spinal cord, which in turn causes the diffuse delayed discharges characterizing the group II reflex. Figures 7, 8, 9, 10, 11, 12 reveal that the group II multineuron-arc discharges are distributed overwhelmingly to the flexor musculature, as would be expected from the early observations of Sherrington (43). These facts provide ample confirmation for the association, developed by Hughes and Gasser (16), between the cord potentials and the flexor reflex.

The distribution of group II and group III reflexes. The peroneal nerve, considered as a 'motor' nerve, is distributed in the main to muscles of physiological flexion (43). In contrast, the tibial nerve contains motor fibers distributed to posterior tibial and plantar muscles, muscles of physiological extension. As an approximation these nerves may be considered as flexor and extensor nerves respectively, and in practice, no essential distinction, in terms of recorded reflex discharges, has been found between the parent trunk of the peroneal nerve and its constituent branch to the tibialis anterior muscle on the one hand, or between the parent trunk of the tibial nerve and its constituent branches to the gastrocnemius muscle on the other hand. With these considerations in mind, the distribution of activity engendered by stimulation of group II and group III afferent fibers has been examined.

Separation of the group II and group III fibers, the latter comprising essentially the delta fibers, depends primarily upon the strength of stimulation. Figure 7 illustrates the reflex responses recorded from the peroneal

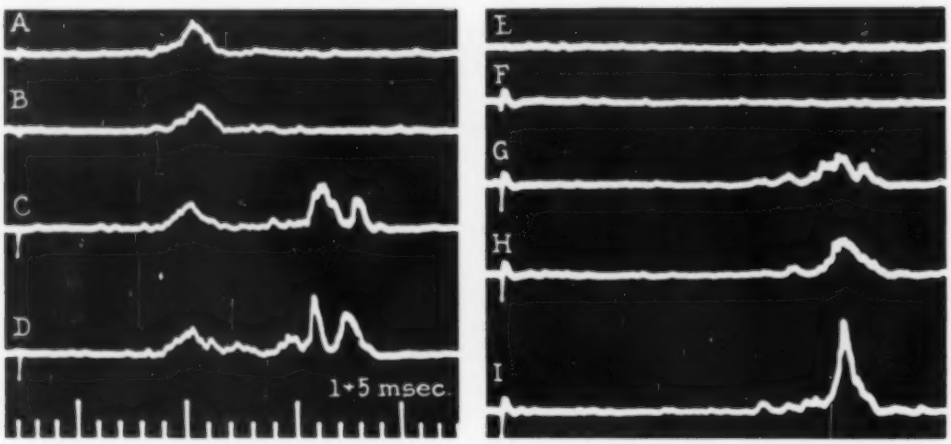

FIG. 7. A, B, C, D—stimulation of sural nerve. A, B—stimulation at group II strength. C, D—stimulation at group III strength. Recording leads on peroneal nerve. E—blank sweep. F, G, H, I—stimulation of gastroc. nerves recording leads to peroneal nerve. F—stimulation at group II strength—no reflex. G, H, I—stimulation at group III strength—group III reflex.

nerve as the result of stimulating the sural nerve (A to D) and the gastrocnemius nerve (F to I). Record E shows the electrical base line in the absence of specific stimulation. The strength of stimulation will be referred to as weak (group II) or strong (group III).

Weak stimulation of the sural nerve (7A, B) results in a reflex discharge into the peroneal nerve with a total latency approximating 6 msec. With strong stimulation, this discharge grouping is present as before, but added thereto is another discharge grouping (7C, D). The latency of the second discharge (group III reflex) cannot be estimated with certainty, but approximates 11 msec. The situation is only slightly different when the gastrocnemius nerve is employed for afferent stimulation, for weak stimulation does not always result in any reflex discharge into the peroneal nerve (Fig. 7F). On strong stimulation of the gastrocnemius nerves, group III reflexes regularly appear in the peroneal nerve (7G, H, I) with the same time relationship as they exhibit on sural nerve stimulation (compare 7G, H, I with 7C, D). It will be remembered that flexor reflexes resulting from stimulation of the gastrocnemius nerves has been described by Sherrington (43) and Eccles and Sherrington (9). Presumably those reflexes frequently belonged to group III of the present classification. The not infrequent absence of group II reflex discharge on stimulating the gastrocnemius nerves is related to the poverty of medium sized afferent fibers (8, 29), but certainly there are sufficient to develop a subliminal field of excitation among the central neuron pools, and upon occasion to provoke a reflex discharge (cf. 21, Fig. 5A).

When the tibial nerve (less its branches to the gastrocnemius muscle) is substituted for the peroneal nerve to serve as an efferent reflex limb, little or no discharge attends stimulation of either sural or gastrocnemius nerves. Typically there is no reflex pathway from the gastrocnemius nerves to the (remainder of the) tibial nerve (Fig. 4H, I; Fig. 8B, C). A slight discharge may be found in the tibial nerve when stimulating the sural nerve; it is not increased apparently by strong stimulation (compare Fig. 8D, E). This last discharge is difficult to interpret; it might represent 'residual ipsilateral extension' or specialized reflex activity directed to the small muscles of the foot through the plantar divisions of the tibial nerve. Since the residual ipsilateral extension reflex is usually a rebound following preliminary inhibition (4, p. 81, Fig. 43), this seems at the moment an unlikely explanation, for the latency would then be much greater.

Since the experiments of Fig. 7 and 8 are performed with the dorsal and ventral root systems of the spinal cord intact, antidromic volleys in the motoneurons ensue whenever a muscle nerve is utilized for 'afferent' stimulation. The untoward effects of the antidromic volleys probably need not be considered when the antidromically activated motoneurons and the reflexly tested motoneurons belong one to the peroneal nucleus, the other to the tibial nucleus (32), but as between the divisions of the tibial nerve care must be exercised in forming conclusions. It has been shown above that the

antidromic volley would not seriously impede two-neuron-arc discharges coursing simultaneously through neighboring motoneurons, but this relative immunity need not extend to the group II and group III reflexes, for with their greater central latency they might find the motoneurons well advanced in the course of depression brought on by the antidromic volley in the neighboring motoneurons. The fact that little reflex effect is secured in the tibial nerve on stimulating the purely afferent sural nerve is a partial control, for in this case no antidromic volley is evoked. Furthermore, the number of group II fibers in the gastrocnemius nerves is small, making it unlikely that a substantial group II reflex would be found in the tibial nerve if a way were devised to avoid the antidromic volley. Finally the result of stimulation of cutaneous nerves on extensor muscles (*e.g.*, the vasti, crureus, semimembranosus, anterior part of the biceps femoris, soleus, gastrocnemius) is inhibition (43) rather than excitation (*cf.* also Fig. 12A, B, C). There is reason to believe, however, that a group II or group III reflex would be realized among extensor motor nerves if the extensor inhibitory component of the flexor response evoked by stimulation of the plantar nerves were obviated by the use of natural stimulation (*cf.* discussion on the extensor thrust reflex in connection with Table 2).

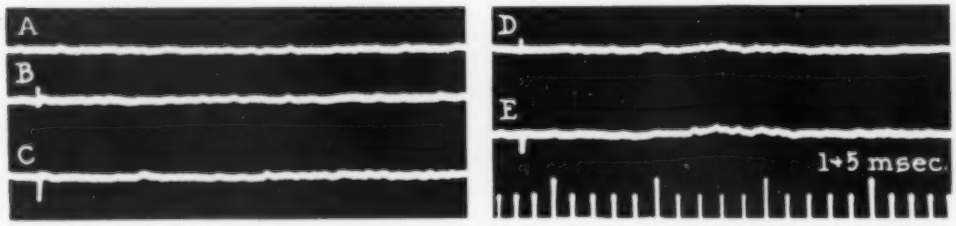

FIG. 8. A, B, C—records obtained from the tibial nerve (less its constituent branches to the gastrocnemius muscle). A—blank sweep. B, C—group II and group III strength stimulation respectively. D, E—stimulation of the sural nerve at group II and group III strength respectively. Note slight discharge in D and E.

The shortest reflex pathway from one peripheral nerve to another. The most powerful reflex discharges transmitted from one hind limb nerve to another are those to be recorded in the peroneal nerve, or a suitable branch thereof, following stimulation of the tibial nerve. Because of this fact the tibial nerve to peroneal nerve reflex has been chosen as the system in which to examine the simplest reflex link from one nerve to another. The simplest link from one nerve to itself is the two-neuron-arc pathway. In order to establish a time reference by which to gauge the minimum central delay of the tibial nerve to peroneal nerve reflex, the group I reflex from the tibial nerve back into itself has been examined. Stimulation and recording leads are arranged so that the conduction distance for the two reflexes is comparable. Figure 9 illustrates an experiment performed after this manner. In observations A and G of Fig. 9 are shown the reflex into the tibial nerve on stimulation of that nerve (compare with Fig. 3). The latency of the two-neuron-arc reflex is

approximately 3.8 msec. Observations B and H illustrate the onset of reflex discharge into the peroneal nerve on stimulation of the tibial nerve. The latency of the first action is approximately 5.3 msec., *i.e.*, 1.5 msec. longer than that to be expected on transmission through two-neuron-arc pathways. It is obvious that the reflex discharge resulting from a single stimulation need not necessarily be transmitted through the shortest available pathway (*cf.* 10). Accordingly the discharge through the tibial nerve to peroneal nerve pathway has been examined under conditions of repeated stimulation calculated to yield the greatest facilitation of the response to the second of two successive shocks. A stimulation interval of 3.0 msec. was found to be most effective. In Fig. 9C,–F and I–L, the responses to single and double stimulation are presented in alternation, the single responses being those to the first of the two shocks to the tibial nerve. By this plan one may judge the approximate electrical base line upon which is written the facilitated responses to the second shock. A prominent peak appears in records D, F, J, L with a latency of 4.9 msec. as measured from the time of the second shock. Comparison of the facilitated responses D, F, J, L with the control responses B and H shows that the latency of the reflex into the peroneal nerve is reduced by 0.4 msec. due to the action of the antecedent stimulation. On the other hand comparison of records D, F, J, L with records A and G shows that the latency of the reflex into the peroneal nerve, in spite of powerful facilitation, is 1.1 msec. longer than that of the two-neuron-arc reflex back into the tibial nerve.

The latency differential between the two reflexes under consideration is not all referable to difference in central latency, for the reflex in the tibial nerve results from stimulation of group I afferent fibers, while the reflex in the peroneal nerve results from stimulation of group II afferent fibers. The proper correction for the differential afferent conduction under the conditions of the experiment illustrated in Fig. 9 amounts to 0.5 msec., or a little less (*cf.* also Fig. 5). Then, with allowance of 0.5 msec. for the slower afferent conduction of the reflex into the peroneal nerve, there remains a latency differential of 0.6 msec. between the two reflexes, all of which is attributable to excess central latency. Since this value is appropriate for the delay occasioned by a single synaptic relay (27), it appears that the minimum reflex pathway from the tibial nerve to the peroneal nerve contains one more neuron in series than does the reflex pathway back into the tibial nerve, and is, therefore, a three-neuron-arc pathway. Since the reflex pathway from the tibial nerve to the peroneal nerve contains all the paths pertaining to the classical reflex of the ankle flexor as studied by Eccles and Sherrington (10), it follows that the minimum pathway for this flexor reflex proper is one of three neurons.

Group I and group II reflex discharges into flexor nerves. Although the shortest pathway mediating the flexor reflex proper is one of three neurons (Fig. 9), the motoneurons of flexor muscles are supplied directly by primary afferent fibers and under the appropriate experimental conditions, two-

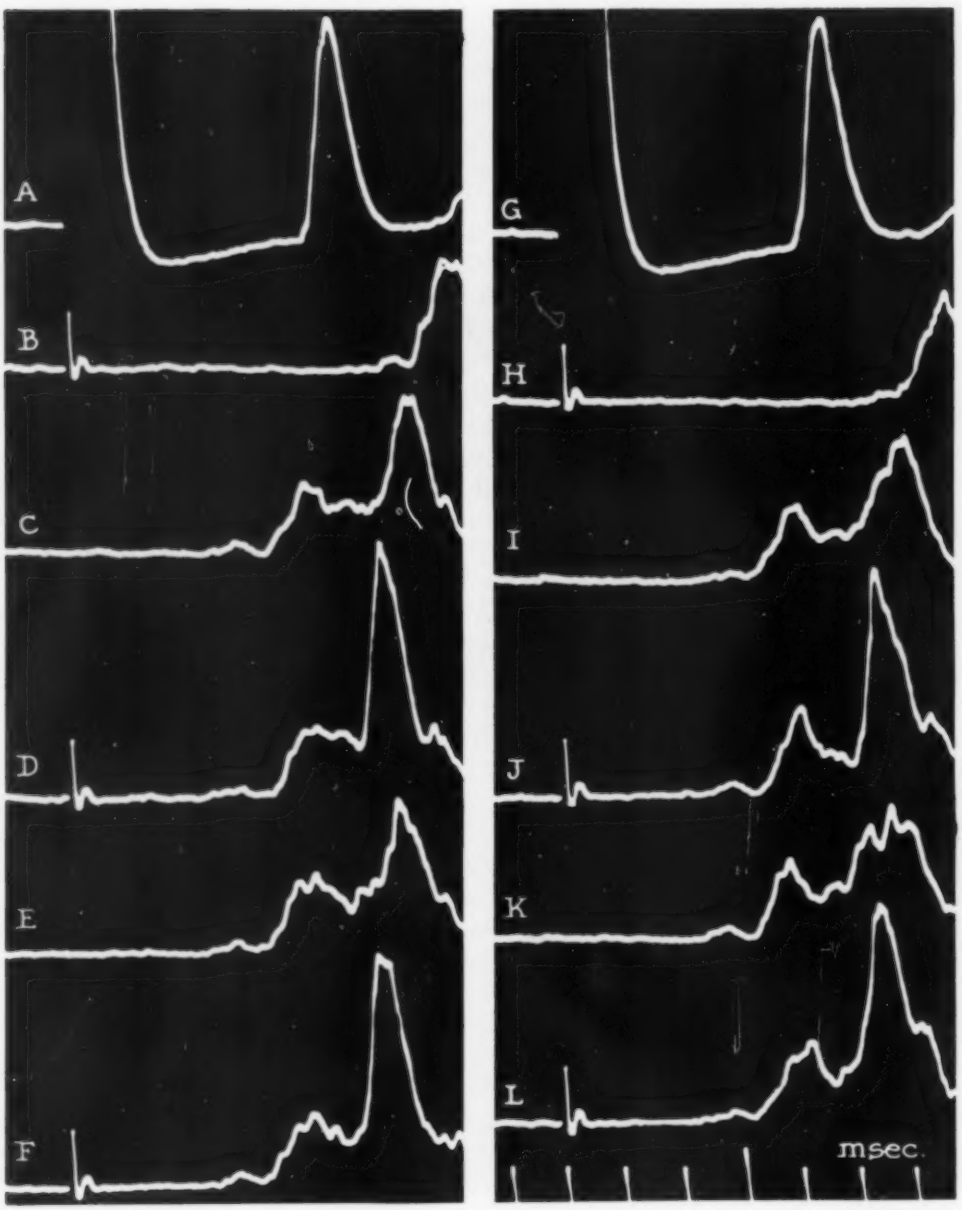

FIG. 9. Reflex discharges on stimulation of the tibial nerve. A, G—the group I reflex recorded on the tibial nerve as in Fig. 3. B, H—onset of group II reflex recorded on the peroneal nerve. In D, F, J, L the reflex into the peroneal nerve is facilitated by an antecedent shock to the tibial nerve, the reflex response to which is seen in C, E, I, K. Comparison of the latency of the facilitated reflex in the peroneal nerve with that of the reflex in the tibial nerve indicates that the minimum central pathway between the tibial nerve and the peroneal nerve contains an interneuron in series.

neuron-arc reflex discharges may be demonstrated in flexor nerves. The experimental conditions are those by which similar discharges may be recorded in the extensor paths (Fig. 1, 3, 9).

Figure 10 illustrates the reflex discharges to be found in the nerve to the tibialis anterior muscle on stimulation of the tibial nerve and the peroneal

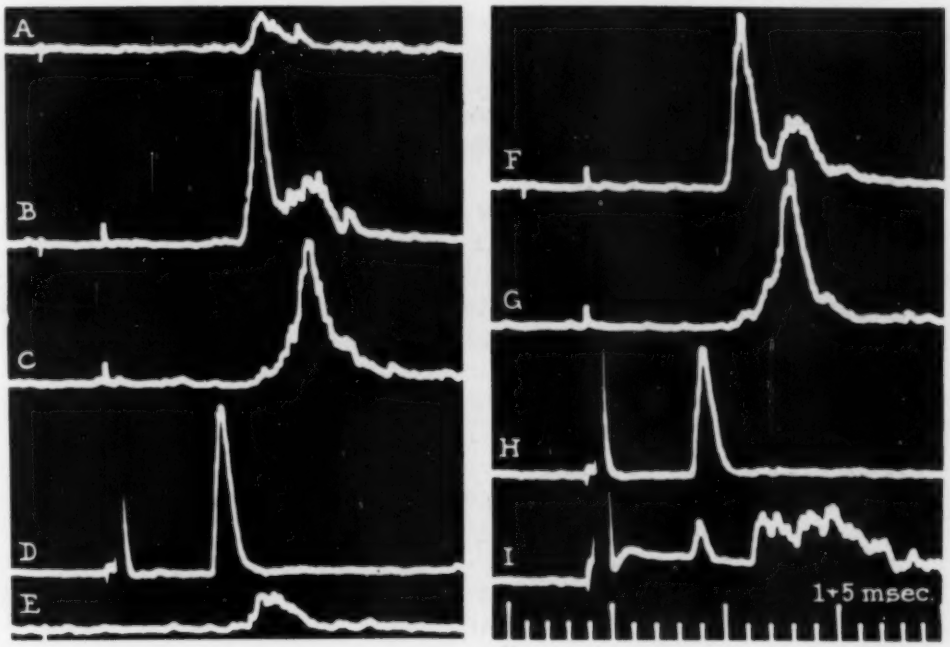

FIG. 10. Reflex discharges into the nerve to the tibialis anterior muscle (ankle flexor). A,E—submaximal group II reflex evoked by stimulation of tibial nerve. C, G—maximal group II reflex evoked by stimulation of the tibial nerve. B, F—facilitated reflex by combined stimulation of the tibial nerve. D, H—group I reflex evoked by stimulation of the parent trunk of the peroneal nerve at approximately half maximal group I strength. I—when the peroneal nerve shock is increased the group I reflex volley is diminished by the consequently greater antidromic volley and group II (and group III) reflex discharges appear *de novo*.

nerve (the latter being the parent trunk for the nerve to the tibialis anterior muscle). Observations A, C, E, G show the reflex discharges resulting from single shock stimulation of the tibial nerve, the shock being stronger for C and G than for A and E. Observations B and F present the result of combined stimulation of the tibial nerve, the stronger shock preceded at an interval of approximately 3.0 msec. by the weaker shock. Comparison of B and F with C and G shows that the latency of the response to the second tibial nerve shock is shortened by 0.8 msec. to a value of 5.8 msec. In contrast, stimulation of the parent trunk of the peroneal nerve results in a group I (two-neuron-arc) reflex into the nerve to the tibialis anterior muscle (Fig. 10D, H). The latency for this group I reflex is 4.6 msec. The reflex pathway from the stimulating electrodes through the spinal cord and back to the recording

leads on the nerve to the tibialis anterior muscle approximates 38 cm., or 7 cm. longer than the total reflex pathway obtaining in the experiment illustrated in Fig. 3. The additional latency (0.6 msec.) of reflex 10D, H over that of reflex 3A is only sufficient to account for conduction through the additional 7 cm. length of pathway at a velocity of 117 M/sec. Again, the records 10D, H were obtained by the use of shocks submaximal for the group I fibers of the peroneal nerve. This is shown by the fact that the group I reflex is decreased on increasing the strength of stimulation, due to the increase in the antidromic volley, and consequent extension of central refractoriness (compare H with I in Fig. 10). Also, with the increase in strength of the peroneal nerve shock, group II reflex discharges appear in the nerve to the tibialis anterior muscle.

The peroneal nerve is a mixed nerve. The low threshold reflex appearing in the nerve to the tibialis anterior muscle on stimulation of the peroneal nerve does so by virtue of the stimulation of afferent fibers arising in the tibialis anterior muscle, for, stimulation of the peroneal nerve after segregation of the tibialis anterior nerve results only in delayed discharges into the latter (*cf.* Table 1). Conversely the late discharges seen in record I of Fig. 10 must be due largely, but not exclusively, to the stimulation of cutaneous afferent fibers reaching the peroneal nerve trunk through its superficial branch. Thus the initial discharge into the tibialis anterior muscle, on stimulating the parent peroneal trunk has the latency, threshold, and distribution features to be expected of a group I reflex. In this connection it will be noted that Sherrington (38), Asayama (1) and Denny-Brown (5) have described the tendon-jerk, or 'pluck' reflex in flexor muscles, and that Forbes Campbell and Williams (11) and Matthews (28) have demonstrated afferent responses to stretch of flexor muscles. Since the two-neuron-arc reflex does not appear in the pathway of the flexor reflex, there is ample reason to regard the two-neuron-arc connections of flexor muscles as devoted to the mediation of the tendon-jerk or 'pluck' reflex exhibited by those muscles.

In connection with Fig. 9 and 10 it has been seen that the latency of the group II reflex discharges is shortened by antecedent stimulation, as would be expected from the experiments of Eccles and Sherrington (10). In the absence of antecedent stimulation discharges through the three-neuron-arc pathway of the group II flexor reflex are almost (Fig. 9B, H) or quite absent (Fig. 4M, 7, 10) *i.e.*, subliminal, when the afferent stimulation is applied to a peripheral nerve, even though this stimulation be powerful, But, just as flexor reflex activity is shunted into the shorter available paths by facilitation (Fig. 9, 10), so is it similarly advanced by shifting the site of afferent stimulation from a peripheral nerve to a dorsal root.

Figure 11 presents an experiment in which are compared the reflex discharges into the deep peroneal nerve by stimulation of the tibial nerve, the S1 dorsal root and the L7 dorsal root. The deep peroneal nerve supplies the tibialis anterior, extensor longus digitorum and extensor brevis digitorum, all three of which respond in the great flexion reflex (43). It is a convenient nerve

structure for the recording of flexor activity. As a preface to the consideration of Fig. 11, one should bear in mind the differences between the L7 and S1 spinal segments in relation to the three muscles served through the deep peroneal nerve. The L7 segment regularly supplies the muscles mentioned (35, 10). The S1 segment may contribute a small twig to the peroneal nerve when the arrangement of the plexus is of the postfixed type. One would ex-

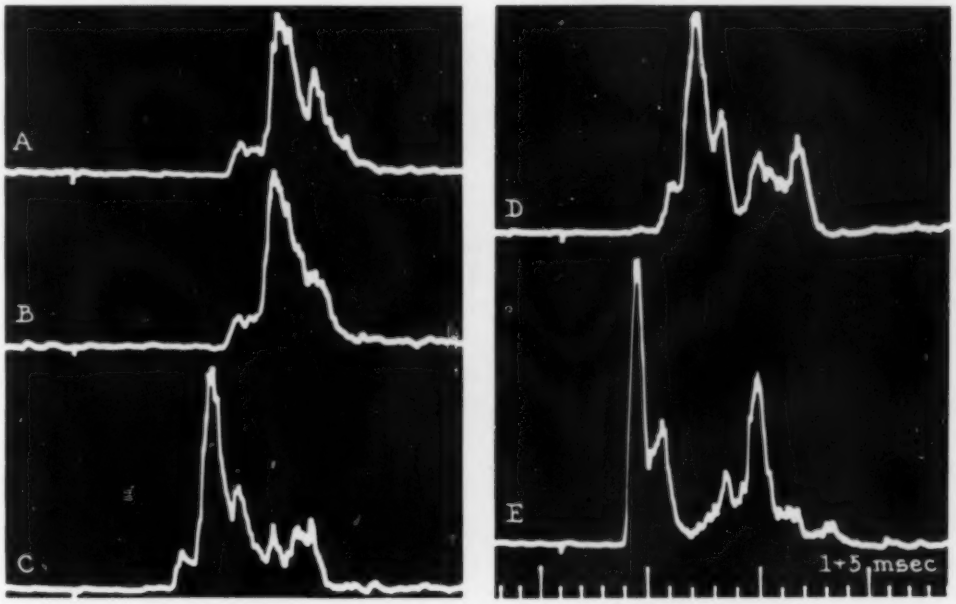

FIG. 11. Reflex discharges into the deep peroneal nerve (supplying MM. tibialis anterior, extensores longus et brevis digitorum). A, B—reflex discharge on stimulation of the tibial nerve, C, D—reflex discharges on stimulation of the S1 dorsal root. E—reflex discharge on stimulation of the L7 dorsal root. Note 'synapse skipping' and concentration of activity through shorter reflex chains when stimulation is advanced from peripheral nerve to dorsal root, also threshold two-neuron-arc discharge when stimulating S1 dorsal root compared with powerful two-neuron-arc discharge when stimulating L7 dorsal root.

pect to find, therefore, little (postfixed preparation) or no (prefixed preparation) two-neuron-arc reflex discharge from the S1 dorsal root to the deep peroneal nerve, but a not inconsiderable two-neuron-arc discharge from the L7 dorsal root to the deep peroneal nerve.

Figure 11A and B illustrates the reflex discharge recorded from the deep peroneal nerve on stimulating the tibial nerve. The latency of this discharge is approximately 7 msec. Observations C and D illustrate the reflex discharge similarly recorded, on stimulating the S1 dorsal root. As might be expected there is a small, but quite regular two-neuron-arc discharge appearing after a latency of 3.2 msec. (compare C and D with E, obtained by stimulation of the L7 dorsal root, and which contains a powerful two-neuron-arc discharge). The arrangement of the plexus in this preparation was postfixed, and direct fiber connection between the deep peroneal nerve and both the S1 dorsal root

and S1 ventral root was proved by the recording of directly conducted alpha spike potentials between the nerve and the roots. Disregarding the two-neuron-arc discharge in C and D for the moment, for this represents reflex activity arising from the deep peroneal nerve rather than the tibial nerve, the latency of the next discharge in order is 4.4–4.6 msec., encompassing some slight variation from one observation to another. On advancing the site of stimulation from the tibial nerve to the dorsal root, therefore, the latency of the flexor reflex proper is reduced from 7 msec. to approximately 4.5 msec. Some fraction of this latency differential is referable to the shortening of the afferent limb of the reflex. Since the tibial nerve contains group I fibers in addition to the group II fibers mediating the reflex in question, the exact allowance for afferent conduction cannot be measured. Assuming that as much as 1.7 msec. afferent conduction time is involved (this would represent 12 cm. conduction at 70 M/sec.) there is still a shortening of central latency amounting to 0.8 msec., which occurs by virtue of 'skipping a synapse' (26).

The most prominent discharge peak in C and D of Fig. 11 has a latency of 5.6 msec., which is shorter than that of the initial discharge in A and B only by the equivalent time for conduction from the tibial nerve to the S1 dorsal root. It would seem that this peak in C and D represents the same 'order' of reflex discharge as the initial discharge in A and B, but it has gained greatly in potency.

The effect of advancing the site of stimulation from the peripheral nerve to the dorsal root, then, is an intensification of the discharge through the shorter available paths at the expense of discharge through the longer paths, in addition to the simple shortening of latency due to shortening the afferent limb of the reflex pathway. It seems probable that a decrease in central latency brought about in this manner accounts for the apparent long afferent conduction time and correspondingly short minimum central reflex time calculated for the flexor reflex by Eccles and Sherrington (10), for they measured the afferent time by the difference in reflex latency when stimulating the tibial (popliteal) nerve and the S1 (8th post-thoracic) dorsal root.

On the conditioning of two-neuron-arc reflexes. According to the evidence of the present experiments, the segmental reflex discharge is constituted of two-neuron-arc discharge directed in varying ratio, depending upon the segment employed and other considerations, to muscles of flexor and extensor action, together with multineuron-arc discharges almost exclusively directed to muscles of physiological flexion, irrespective of the segment employed. Some of the vagaries of conditioning experiments in which segmental two-neuron-arc reflex discharges are employed as test volleys are undoubtedly due to the dual nature of those discharges. It is frequently found, on causing a two-neuron-arc volley to fall during the multineuron-arc discharge in response to an antecedent shock, that the two-neuron-arc volley is subjected simultaneously to temporal facilitation and spatial inhibition. The explanation for this anomalous behavior becomes clear when the components of the

segmental reflex are segregated as in the experiment presented in Fig. 12. The extensor two-neuron-arc component is obtained by stimulating the nerves to the gastrocnemius muscle, the flexor two-neuron-arc component by stimulating the deep peroneal nerve, and the multineuron-arc component by stimulating the sural nerve. Records are obtained from the L7 or S1 ventral root.

Record A of Fig. 12 shows the extensor two-neuron-arc reflex recorded from the S1 ventral root following stimulation of the gastrocnemius nerves.

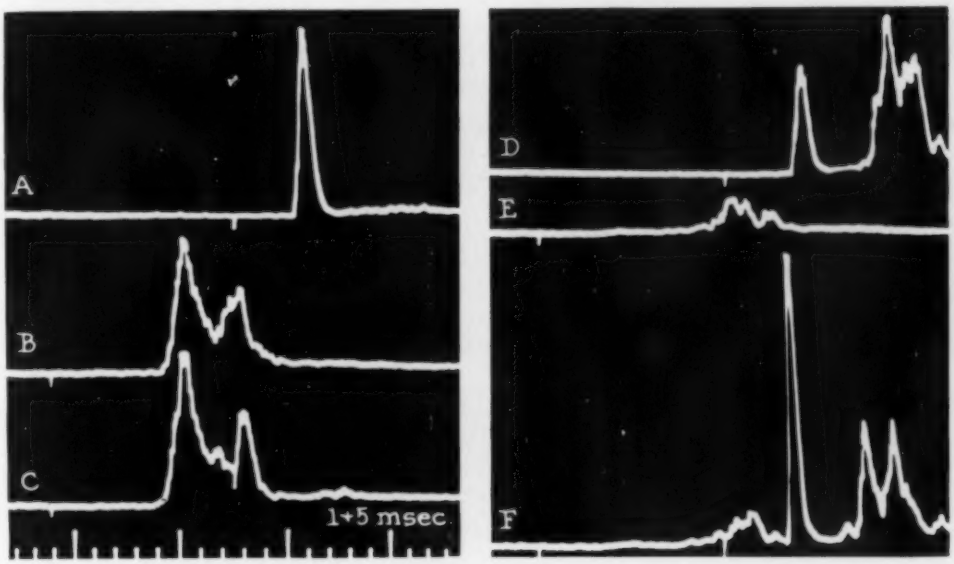

FIG. 12. Conditioning of extensor two-neuron-arc and flexor two-neuron-arc reflexes by stimulation of a cutaneous nerve (sural). A, B, C recorded from the S1 ventral root. A—gastroc. nerves stimulated. B—sural nerve stimulated. C—combined stimulation of sural and gastroc. nerve at interval of 8.5 msec. The gastroc. two-neuron-arc is inhibited, D, E, F—recorded from the L7 ventral root. D—deep peroneal nerve stimulated—note two-neuron-arc and later discharges. E—sural nerve stimulated. F—combined stimulation of sural nerve and deep peroneal nerve. The two-neuron-arc reflex is facilitated both spatially and temporally by the action of the sural nerve volley.

Record B shows the multineuron-arc discharge resulting from stimulation of the sural nerve. On combining these two stimulations (record C) at an interval of 8.5 msec. the extensor two-neuron-arc reflex is inhibited, although few if any extensor motoneurons could have discharged in the earlier reflex. Record D illustrates the response recorded from the L7 ventral root on stimulation of the deep peroneal nerve. The two-neuron-arc discharge is here followed after an interval by multineuron-arc discharges. Record E shows the response evoked by stimulation of the sural nerve. In record F, sural and deep peroneal nerve stimulation are combined as were the sural and gastrocnemius nerve stimulations in 12C. In this case, however, the flexor two-neuron-arc discharge is facilitated, both temporally and spatially.

Similar results can be obtained when stimulating dorsal roots while segregating the extensor and flexor components on the motor side (*cf.* also 33), but the method here illustrated seems preferable in theory for the input to the spinal cord is restricted so that only the flexor or the extensor testing two-neuron-arc discharges are elicited, depending upon choice. On the contrary, when segregation is effected on the motor side, stimulation of dorsal roots will cause activation of both flexor and extensor two-neuron-arcs in parallel, and although only one or the other is recorded, the way is open for undesirable interaction, and the possibility of confusion phenomena within the testing system remains.

The classification of ipsilateral hind limb reflexes. Throughout most of the present paper the reflex discharges described have been classified according to the arbitrary groups outlined in the introduction, but certain obvious correlations with hind limb reflexes as they are known on the basis of motor performance have emerged. Table 2 forms a summary of these correlations and of the foregoing experiments.

Table 2. The classification of ipsilateral hind limb reflexes

Group	Approximate afferent fiber range	Central connections	Origin	Destination	Type of reflex
I	20–12μ	Direct, or two-neuron-arc reflexes	(a) extensor muscles	The extensor muscle from which it arises	Myotatic reflex (the tendon-jerk)
			(b) flexor muscles	The flexor muscle from which it arises	Flexor tendon-jerk (the pluck reflex)
II	12–6μ	Multineuron-arc reflexes. Three-neuron-arc minimum	(a) skin	flexor muscles	The flexion reflex
				extensor muscles (slight)	Residual ipsilateral extension ?
			(b) muscle (slight)	flexor muscles	The flexion reflex
III	6–1μ	Multineuron-arc reflexes. ? minimum	(a) skin	flexor muscles	'Delta' flexion reflex
			(b) muscle	flexor muscles	'Delta' flexion reflex
IV	unmyelinated (C) fibers				(*cf.* 3, 2)

It will be seen at once that the outstanding omission from Table 2 is the ipsilateral reflex of extension known as the extensor thrust (40). This reflex is elicited by pressure or 'deep touch' on the planta (37, 39), whereas nocuous stimulation of the same area elicits flexion of the limb. The plantar nerves are essential to the transmission of the extensor thrust reflex (39), and hence mediate the afferent limb of this reflex. Yet stimulation of these nerves themselves yields flexion (42), accompanied by relaxation of extensors. The extensor reflex is presumably inhibited by the concomitant and prepotent flexor reflex. The extensor thrust seems, therefore, not to be a group I reflex, for with simultaneous combination a group I reflex would outstrip the flexion reflex and thereby escape inhibition. One would expect the extensor thrust to belong in group II. Undoubtedly more prominent group II discharges to extensor muscles would be found in the fore limb, in which the stimulation of digital nerves promotes ipsilateral extension (6). Considerations such as these invoke again the problem to which there is still no decisive answer: it is not yet known to what extent fractionation of spinal centers is determined by anatomical limitation of neuron connections, or to what extent it is attained primarily by functional means, with direct inhibition possibly playing a dominant role.

Summary

The reflex function within the hind limb of myelinated afferent fibers has been examined. Three sub-groups of these fibers are recognizable. The large fibers form direct connections with the motoneurons, the medium and small fibers connect with interneurons.

Reflex discharge mediated through the direct (two-neuron-arc) connections reflects only into the muscle, head of a muscle, or combination of muscles, the large afferent fibers of which are subjected to stimulation. Because of the identity of distribution holding for the two-neuron-arc discharge and the myotatic reflex, it is concluded that the two-neuron-arc pathways are reserved for mediation of the myotatic reflex.

Multineuron-arc discharges, evoked by stimulation of medium and small afferent fibers, are directed for the most part into the nerves of flexor muscles, and represent the flexor reflex proper. The minimum central pathway devoted to this reflex is one of three neurons.

Under appropriate conditions the flexor muscles receive excitation through arcs of two neurons as well as through the multineuron reflex arcs. The conditions are exactly those governing the transmission of two-neuron-arc excitation to extensor muscles. It is concluded that the flexor two-neuron-arc reflex represents the flexor tendon-jerk, or 'pluck' reflex in contradistinction to the flexor reflex proper.

The segmental reflex discharge recorded from a ventral root on stimulation of the dorsal root of the same segment contains three major elements, an extensor two-neuron-arc, a flexor two-neuron-arc and flexor multineuron-arc discharges. Reflex activity through extensor two-neuron-arcs is inhibited,

that through flexor two-neuron-arcs facilitated by the transmission of multineuron-arc reflex action.

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CONDUCTION AND SYNAPTIC TRANSMISSION OF THE REFLEX RESPONSE TO STRETCH IN SPINAL CATS

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IN THE PRECEDING PAPER (14) it was found that the reflex discharge provoked by stimulation of the large (20–12μ), low-threshold muscle afferent fibers, and transmitted through arcs of two neurons (12) possesses the characteristic and restricted distribution of the myotatic reflex (9). The identity of distribution was so rigidly maintained that it seemed justifiable to attribute to the two-neuron-arc pathways the mediation of myotatic reflexes. The concept, of course, is not new (8), but the older evidence in support of the concept lost weight with the advent of more precise measurements of the delay involved in synaptic transmission. Furthermore, one is constantly aware of the danger inherent in drawing conclusions as to natural reflex performance from experiments utilizing electrical stimulation of bare nerve trunks. Therefore, the conclusion derived from such experiments could be sustained and accepted only if the myotatic reflex evoked by the appropriate natural stimulus, *viz.*, stretch, were found, on reinvestigation, to have the same characteristics of conduction and synaptic transmission as the two-neuron-arc reflex discharge obtained by stimulation of muscle nerves. The present experiments were designed to examine the temporal course of the reflex response to phasic stretch. Some of the observations were mentioned briefly in a preliminary note (13).

The experiments were performed on cats made spinal by transection accomplished through the atlanto-occipital membrane. Following transection artificial respiration was instituted and the ether anaesthetic discontinued. The pelvis was fixed by heavy pins, the femur and tibia by drills. These were held by heavy standards which were firmly attached to the operating platform, of two-inch oak, supported by three-inch I-beams on a sand-filled oak table. Satisfactory fixation of the muscle origins was thus obtained. The stretching mechanism was similarly mounted on another sand-filled table. The use of two such tables separated by an air gap prevented the direct transmission of mechanical jar to the preparation. A hooked steel wire impaling the tendon of the gastrocnemius muscle served to connect it to the stretch mechanism, which consisted of a plunger operated by two solenoids arranged in opposition to each other. The solenoids were activated by condenser discharges timed by the usual stimulating circuit. One solenoid was arranged to pull, through the steel wire, on the freed tendon of the muscle. The other served to check the first so that the extent and duration of the stretch could be limited. In order to overcome inertia, the solenoid plunger was allowed to gain its momentum before acting upon the wire affixed to the tendon. A break contact on this wire fed an impulse to the amplifier to signal the onset

of stretch-movement. The time relations of the movement were recorded by the use of a photoelectric cell. Although the mechanism is not as flexible as one might desire, it behaved in a constant manner for any given setting of the controls, and served the immediate purpose of producing a brief stretch synchronized with the sweep of the cathode ray oscillograph.

The gastrocnemius muscle was employed for all the present observations. The tendon together with its insertion into the tuberosity of the calcaneus was fully isolated and freed from the insertion of the soleus muscle. Extensive denervation of the limb was regularly practised. Since the ventral roots were cut for the purpose of recording the reflex responses, the muscle itself was unable to participate in the reflex response. This arrangement is particularly useful, for the jerk reflex proper is divorced from all secondary phenomena such as the response to active tension, the myotatic appendage and incipient clonus.

Figure 1 illustrates stretch-evoked afferent discharges recorded from the nerve to the medial head of the gastrocnemius muscle. Records A, C, E show, by photoelectric recording, the extent and duration of the stretch-movement imparted to the gastrocnemius tendon to provoke the afferent discharges recorded in B, D, F respectively. The afferent discharge 1B is caused by a stretch of 1 mm. effected in 4.0 msec. It will be seen that the recognizable

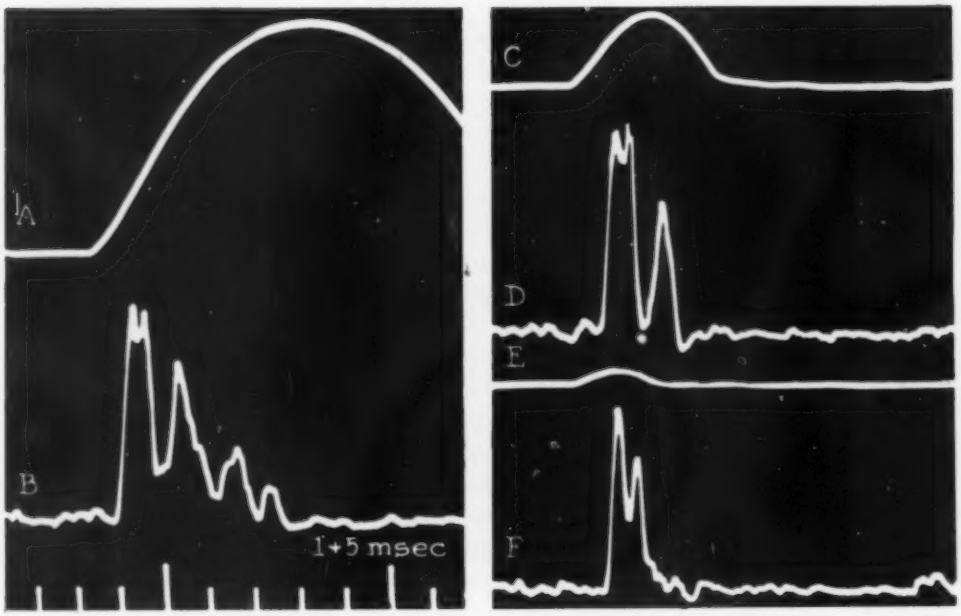

FIG. 1. Afferent responses to brief stretch of M. gastrocnemius recorded from the nerve to the medial head of that muscle. In A, C, E are recorded the extent and duration of the stretches employed to obtain the responses B, D, F respectively. The extent of stretch indicated in A is 1 mm.; in C, 0.3 mm.; in E, 0.05 mm. Most of the observations illustrated in this paper were obtained by the use of 0.2–0.3 mm. stretches. Time in 1 and 5 msec. intervals.

discharge occurs during the period of stretch-movement, and takes the form of a succession of imperfectly synchronized volleys. When the stretch is reduced to approximately 0.3 mm. effected in 1.7 msec., the afferent discharge, 1D, is correspondingly reduced in duration. The last two discharge peaks present in 1B are no longer realized, and the second peak is reduced in amplitude. The initial discharge peak, however, is intact. Further reduction of the stretch to approximately 0.05 mm. causes a further reduction in the afferent response, 1F, only the initial discharge remaining; this is decreased and further 'splintered.' The degree of stretch employed for response 1F is still well above threshold. It will be remembered that Denny-Brown and Liddell (3) obtained a jerk reflex in the decerebrate supraspinatus muscle with a stretch of approximately 8μ.

In the records illustrated in Fig. 1 there is a degree of diphasicity which results in emphasis of the relatively synchronous discharges of stretch-movement over the asynchronous activity apparently maintained throughout the period of muscle elongation. The latter discharges are seen to better advantage in Fig. 5B and 6B.

The latency of the afferent discharge as recorded in Fig. 1 approximates 0.7 msec., of which a considerable fraction is consumed in simple conduction. A number of attempts to obtain a valid estimate of 'end-organ delay' have been made. In a typical experiment the afferent response to stretch is first recorded. Then, with stimulating electrodes buried in the heart of the muscle belly, the preterminal nerve bundles are stimulated, the conducted action being recorded as before. The latency of the naturally evoked volley is longer than that of the electrically stimulated volley by as little as 0.2–0.3 msec. The electrically stimulated volley is conducted, of course, in both afferent and motor fibers, but this fact has no practical bearing on the outcome of the experiment for as will be seen in connection with Fig. 2 and 3, the afferent impulses provoked by sudden stretch travel in the forefront of the action potential of the mixed nerve. Values obtained by this method must be maximal rather than minimal values, for error due to possible spread of the stimulus or improper placement of the stimulating electrodes would decrease the apparent conduction time for the electrically stimulated volley, and by subtraction this would increase the apparent latency of the stretch response.

Some fraction of the 'excess latency' of the stretch-evoked response is needed for transmission of the tension wave from the free end of the tendon to the site of the first-responding receptors, wherever that may be. Another small fraction of time must be allocated for conduction from the point at which the end-organ excites the afferent fiber to the point at which the electrical stimulus excites the fiber. What little time is left probably may be accounted for in terms of a 'temps utile.' Altogether the evidence appears to militate against the view that a specific end-organ delay is involved in the stimulation by stretch of the particular end-organs mediating the initial afferent response. In essence, this is the conclusion reached by Forbes, Camp-

bell and Williams (4), although Jolly's earlier measurements indicated the existence of a true end-organ delay (7).

Figure 2 presents an experiment designed to measure the conduction velocity of the afferent fibers mediating the response to stretch. The afferent discharge was first recorded from the first sacral (S1) dorsal root, severed from its connection with the spinal cord, and subsequently from the tibial nerve in the popliteal space. The conduction distance between the proximal (to the muscle) recording leads of the two pairs was 12 cm. The difference in latency of conduction is 1.025 msec., which yields a conduction rate of 117 M per sec.

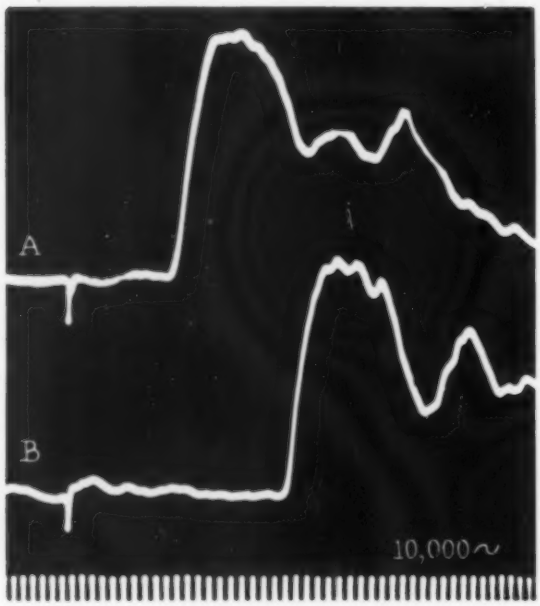

FIG. 2. Conduction of stretch-evoked afferent response. A—afferent response recorded from tibial nerve, B—from S1 dorsal root. Conduction distance—12 cm. Differential latency—1.025 msec. Conduction rate—117 M per sec. Time—10,000 cycles.

In the graph of Fig. 3 are plotted the results of five experiments such as that illustrated in Fig. 2. Each point on the graph represents an experiment, and relates the latency difference between the discharge recorded at two points along the afferent pathway to the conduction length of the pathway between the two recording stations. The observations at short conduction distances were made with both recording stations on the tibial nerve, or on one or both of the nerves to the gastrocnemius muscle. Those observations at long conduction distances were made with one of the electrode pairs on the dorsal root. In two experiments the conduction velocity of a volley evoked by electrical stimulation of the intramuscular branches of the nerve to the medial head of the gastrocnemius muscle was determined in addition. All of the observations from the various preparations fall about a straight-line plot having a slope of 116 M per sec. It follows that fibers mediating the afferent response to stretch fall among those of highest velocity in the muscle nerve. Within the limits of measurement the secondary peaks of the afferent discharge evoked by stretch represent activity in fibers of similar properties (*cf.* Fig. 2). Thus, one criterion for the identification of the myotatic reflex pathway with the two-neuron-arc pathway is satisfied.

Comparison of the afferent discharges encountered in the present experi-

ments with those recorded by Matthews using single fiber preparations (15) suggests that the relatively synchronized volleys of stretch-movement have their origin in the A type receptors, by virtue of low threshold, rapid response and sudden cessation. This would indicate that the muscle spindles are the sensient organs originating these discharges.

The succession of afferent discharge peaks may represent the successive recruitment of end-organs to the active 'pool,' or the repetitive discharge of end-organs recruited at the onset of stretch movement. In the latter case the rate of firing would approach 1000/sec., if the discharge peaks represent the rate, and not a multiple of the rate, of the individual end-organ discharges. This figure seems high, but the nerve fibers are capable of responding at such rates, for a short time at least (6). Employing the single fiber technique, the highest discharge rate observed by Matthews (15) was 500/sec. during a stretch of 5 mm. at the rate of 25 cm./sec. The highest rate of stretch attained in the present experiments was approximately 35 cm./sec. over a shorter distance, so it is possible that a higher rate of firing was induced. Since the stretch-movement usually lasted 2–3 msec. some repetitive discharge certainly would have occurred, but successive recruitment is not thereby eliminated.

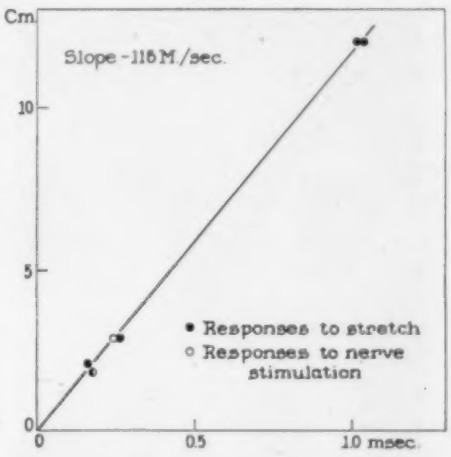

FIG. 3. Graph to show average conduction rate of afferent response to stretch in five experiments. Each point represents the difference in latency of the afferent response recorded at two points along the afferent pathway (as in Fig. 2) plotted against the conduction distance between the two points. For two of the experiments the conduction rate for an electrically stimulated volley is plotted. Average maximum conduction rate—116 M per sec.

In order to examine the central latency of the reflex response to stretch the following procedure was adopted. The reflex was first recorded from the S1 ventral root. This appears in the inset of Fig. 4 and again in 4C. Only the initial volley is to be seen in Fig. 4C. The S1 dorsal root was then stimulated at a shock strength which yields a two-neuron-arc reflex discharge of approximately the same size as the initial stretch-evoked reflex volley. A record of the segmental two-neuron-arc reflex volley is found in 4B. The dorsal root was then severed at its junction with the spinal cord and equipped with recording leads. The proximal (to the muscle) recording lead was placed as close as possible to the point occupied by the cathode of the stimulating pair employed to obtain record 4B. With this disposition of leads the afferent response to the stretch was recorded; this is found in 4A. Now, if the initial volley of the stretch-evoked reflex is indeed transmitted through arcs of two neurons as predicted (14), the sum of the latencies in 4A and 4B should ap-

proximate the latency in 4C ,which it does to within 0.1–0.2 msec. The slight additional latency of the naturally evoked reflex is referable to the greater dispersion of the afferent volley caused by long afferent conduction and natural stimulation. The initial reflex discharge in response to stretch, then, is transmitted through arcs of two neurons.

The initial volley of the stretch-evoked reflex is followed at an interval of approximately 0.8 msec. by a second reflex volley, which is much larger than the first. The second volley like the first is transmitted through arcs of two neurons. Figure 5A, B, C illustrate in order the time relations of stretch, the afferent response recorded from the gastrocnemius nerves, and the reflex response recorded from the S1 ventral root in another preparation. The latency of the initial reflex volley is approximately 3.9 msec., that of the second reflex volley 0.8 msec. longer. Since there are two clearly defined successive afferent discharges impinging upon the spinal cord (5B), one would expect to realize two reflex volleys. Furthermore, the interval between the two reflex volleys is equal to or very slightly less than the interval between the two afferent volleys (compare 5B and 5C). This being so the central delay of the second reflex volley is of the same order of magnitude as that of the first reflex volley.

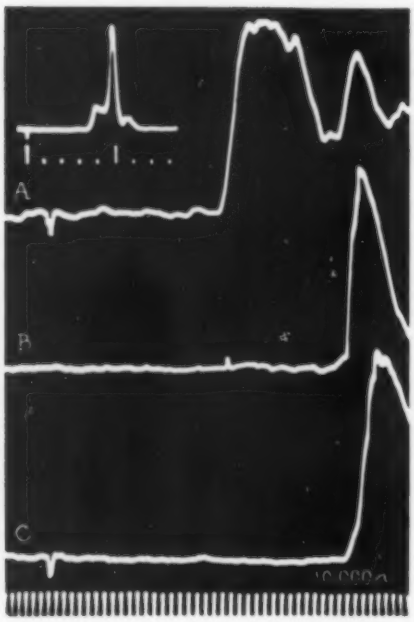

FIG. 4. Reflex latency of the response to brief stretch. A—afferent response recorded from the S1 dorsal root. B—segmental two-neuron-arc reflex (stimulus S1 dorsal root, recording S1 ventral root). C—reflex evoked by stretch. The sum of the latencies in A and B approximates that of C, showing that the initial reflex response to stretch is conducted through arcs of two neurons. Inset—the complete reflex response in this experiment consists of three successive volleys. Time for A, B, C—cycles. Time for inset in 1 and 5 msec. intervals.

The latency differential between the two successive reflex volleys is not sufficiently long to admit the possibility that the second reflex volley is evoked through three-neuron-arc pathways by the action of the afferent impulses set up at the very beginning of stretch. The three-neuron-arc reflex discharge results from the stimulation not of group I fibers, but of group II fibers (13). When the two groups of fibers are stimulated in the thigh, the group II volley reaches the spinal cord 0.4 msec. after the group I volley, the conduction distance being 12 cm. (14, Fig. 5). The pathway from the mid-belly of the gastrocnemius muscle to the spinal cord is 18–20 cm. in length. Assuming that group II fibers were to participate in the first afferent

response to stretch, the resulting group II volley would reach the cord dorsum at least 0.6 msec. after the group I volley. To this must be addded another 0.6 msec. for the additional synaptic relay of a three-neuron-arc, to give a minimum of 1.2 msec. by which the second reflex volley should trail the initial reflex volley. This minimum value is considerably longer than the observed interval of 0.8 msec.

The discharges mediated through arcs of three neurons are directed into flexor channels (14). It is known from the experiments of Denny-Brown (2) that activity may appear in the tibialis anterior muscle as the result of sudden stretch of the gastrocnemius muscle, but it does so during the heart of the silent period of the extensor muscles. According to Denny-Brown the latency for activity in the tibialis anterior muscle averaged 22.7 msec. compared with 8.6 msec. for the latency of the tendon-jerk reflex in the gastrocnemius muscle itself. The second reflex discharge in the present experiments, and the third when it is present (inset of Fig. 4), is obviously part of the tendon-jerk reflex proper, rather than a contribution to flexor activity associated with the silent period of the extensor muscles. In addition to these considerations there is the fact that the gastrocnemius nerves contain relatively few group II fibers. Group II reflexes of any order are not regularly produced by stimulation of the gastrocnemius nerves (14). For these various reasons it is concluded that the second reflex volley in response to brief stretch, like the initial volley, is conducted through arcs of two neurons.

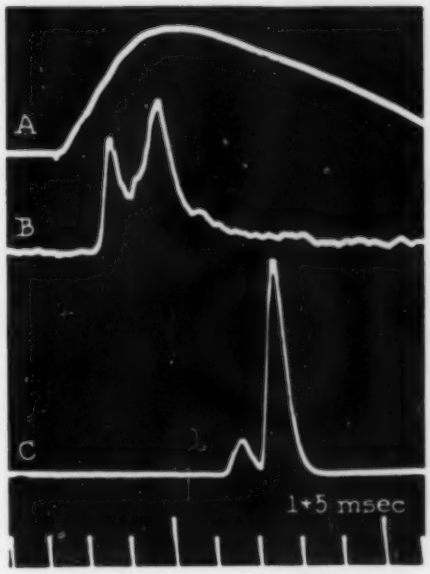

FIG. 5. Tendon-jerk reflex of M. gastrocnemius. A—stretch imposed upon the gastrocnemius muscle. B—afferent response recorded from the gastrocnemius nerves in the thigh. C—reflex response recorded from S1 ventral root. Time in 1 and 5 msec. intervals.

When the stretch produced by the pulling solenoid used in these experiments is unchecked by the opposing solenoid, it may happen that a third reflex volley, of small size, is discharged (*cf.* inset of Fig. 4). This reflex volley occurs later rather than earlier than the hypothetical three-neuron-arc time discussed above, but the other arguments advanced in favor of the view that the second reflex discharge pertains to arcs of two neurons hold also for the third reflex volley when this is in evidence.

The initial afferent volley of the stretch response may prove subliminal for the motoneurons, in which case the reflex volley provoked by the second afferent volley may constitute the whole reflex response. Figure 6 presents

an experiment in which this occurred. Records A, B, C show in order the stretch imposed upon the gastrocnemius muscle, the afferent response recorded from the S1 dorsal root, and the reflex response recorded from the S1 ventral root. Although the afferent response is dispersed over a period equal to that of the stretch, and contains two prominent discharge peaks, the reflex consists of a single volley, no more dispersed than is the response obtained by single shock stimulation of the gastrocnemius nerves (12, 14). The latency for this reflex is approximately 4.9 msec., which is almost identical to the latencies of the second reflex discharges in Fig. 4 and 5. The time relationship between the second afferent discharge peak (6B) and the reflex (6C), moreover, accords with the conclusion that the second afferent volley is the immediate provocative agent for the reflex recorded.

Comment

For the duration of stretch impulses are continually bombarding the motor nucleus at an intensity greater than that maintained during the 'resting posture' of the muscle. Signalling the onset of stretch-movement, and for the duration of stretch-movement, regularly spaced synchronized afferent volleys appear, as though superimposed on a continuum of activity. The first of these afferent volleys may (Fig. 4, 5) or may not (Fig. 6) provoke a discharge of motoneurons. By the time the second afferent volley reaches the motor nucleus conditions have changed. Depending upon the initial reflex discharge a few motoneurons may be refractory, but the greater part of the motor nucleus is more excitable than formerly by virtue of the continued impact of afferent activity. Motoneurons are more readily available to the second afferent volley and a large reflex volley results. The central latency of this volley may be even a little shorter than that of the initial reflex volley (temporal facilitation). Subsequent afferent impulses usually fail to reach motoneuron threshold, due possibly to the number of motoneurons already fired by the immediately preceding volleys. The end result is a reflex discharge of shorter total duration than that of the afferent influx. One must bear in mind the possibility that some of the afferent impulses may mediate direct inhibition (10) rather than excitation to the motor nucleus thus shutting off rather than aiding the reflex, or they may serve to feed ascending paths without concern for the local reflex mechanism. Undoubtedly the reflex picture would be different if the stretched muscle were allowed to participate in the reflex action, as was necessarily the case in earlier work on the tendon jerk which depended largely upon either the action potential of the muscle or upon mechanical registration for a means of recording.

The present experiments associate the large (group I) afferent fibers and two-neuron-arc connections with the mediation of the myotatic reflex. It is not known whether or not the smaller afferent fibers in the gastrocnemius nerves partake in the afferent response to stretch of the degree imposed in the present experiments. With greater extension of the muscle other than the

large afferent fibers might be recruited into the response, possibly bringing into play the lengthening reaction. Of course afferent responses which depend upon active tension would not appear at all in these experiments. Since stimulation of some, at any rate, of the smaller fibers of the gastrocnemius nerve yields reflex discharges directed into flexor nerves (14, Fig. 7), it is a fair assumption that those fibers subserve nociception rather than proprioception. Certainly no responses resembling the group III reflex obtained by strong stimulation of the gastrocnemius nerves (14, Fig. 7) have been realized on the occasion of brief stretch in the present experiments.

The latency of the stretch-evoked reflex at the ventral root in the experiments of this series has varied between 3.6 and 3.9 msec. In order to estimate the minimum total reflex latency for the tendon-jerk of the gastrocnemius muscle it is necessary to add to the latency at the ventral root sufficient time for conduction to the muscle and for neuromuscular delay. The additional motor conduction time is approximately 1.8 msec.: neuromuscular delay is approximately 0.55 msec. (11). The minimum total latency from the onset of stretch to the onset of the muscle action potential *at the end plate zone* would approximate 5.95 msec. This is somewhat shorter than the value 8.6 msec. obtained by Denny-Brown (2). Since this value is based on the known transmission time through the minimum reflex arc, it is not expected that the minimum reflex time for the tendon-jerk can be further reduced, except inasmuch as some muscles are closer, anatomically speaking, to the spinal cord, and would involve less time in simple conduction. Other latency values for the most part have been obtained from the knee-jerk preparation rather than the ankle-jerk preparation (8, 5, 1, 2). The conduction pathway for the knee-jerk is shorter and that reflex should appear with shorter latency. The shortest latency encountered by Jolly was 5.3 msec. (8).

FIG. 6. Tendon-jerk reflex as in Fig. 5, but in another preparation. A—stretch imposed upon the gastrocnemius muscle. B—afferent response recorded from the S1 dorsal root. C—reflex response recorded from the S1 ventral root. The single reflex volley corresponds to the second reflex volley in the experiment of Fig. 5. The initial afferent volley is subliminal for the motoneurons. Time in 1 and 5 msec. intervals.

Summary

The afferent response to brief stretch of the gastrocnemius muscle is mediated by large (group I) fibers at an average maximum velocity of 116 M per sec.

There is little if any true delay at the sensient organs responding to stretch.

The reflex response to brief stretch of the gastrocnemius muscle is transmitted through arcs of two neurons.

It was previously shown (14) that the distribution of two-neuron-arc discharges accords with that of the myotatic reflex. For these several reasons it appears that the two-neuron-arc pathways are reserved for the mediation of myotatic reflexes.

The calculated overall minimum latency for the tendon jerk reflex of the gastrocnemius muscle is approximately 5.95 msec.

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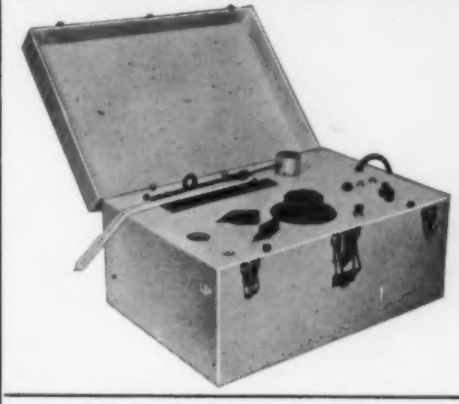

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